# Safety and feasibility between Robotic and laparoscopic D2 radical total gastrectomy for locally advanced gastric cancer: A prospective cohort study（NCT03500471）
# Study protocol

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# Summary

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| Scenario Title | Safety and feasibility between Robotic and laparoscopic D2 radical total gastrectomy for locally advanced gastric cancer: A prospective cohort study（NCT03500471） |
| Scenario Version | V2.0 |
| Sponsor | Peiwu Yu |
| Research Center | Department of General Surgery and Center of Microinvasive Gastrointestinal Surgery, Southwest Hospital, China |
| Indications | Patients diagnosed with gastric cancer who need to received total gastrectomy with D2 lymphadenectomy. (cT2-4a, N0/+, M0) |
| Purpose of research | To investigate the safety and feasibility between Robotic and laparoscopic radical total gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer. |
| Research design | prospective, single-center, non-randomized, controlled, non-blind, and non-inferiority observation trial |
| Case grouping | Group A (Experimental): Robotic-assisted Total Gastrectomy with D2 Lymphadenectomy<br>Group B（Compared): Laparoscopic-assisted Total Gastrectomy with D2 Lymphadenectomy |
| The basis for determining the sample size | This study is a non-inferiority study, with postoperative complications as primary outcome. According to the relevant studies, the postoperative complication rate of laparoscopic total gastric surgery is about 15%.In this study, it was assumed that the postoperative complication rate of the study group was similar to the control group, with $\alpha$=0.05, $\beta$=0.2, and the non-inferiority threshold value set as 15%. PASS 11 was used for calculation, and the sample size of each group was 68 cases. Considering that the maximum detachment rate of this clinical study was 10%, the final sample size was 75 cases in each group. |
| Inclusion criteria | ● Age between 18 and 80 years<br>● Endoscopic biopsy and CT confirmed locally advanced gastric adenocarcinoma, requiring D2 radical gastrectomy.<br>● Preoperative examination showed no absolute contraindication and no distant metastasis<br>● Performance status of 0 or 1 on ECOG scale<br>● ASA class I, II, or III<br>● Written informed consent |

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| Exclusion criteria | ● Enlarged or bulky regional lymph node (diameter over 3cm) supported by preoperative imaging including those surrounding important vessels<br>● Emergency surgery due to complication (bleeding, obstruction or perforation) caused by gastric cancer<br>● Previous upper abdominal surgery (except laparoscopic cholecystectomy)<br>● Previous neoadjuvant chemotherapy or radiotherapy<br>● Unstable myocardial infarction, angina, or cerebrovascular accident within the past 6 months<br>● FEV1 < 50% of predicted values<br>● Other malignant diseases<br>● Severe mental disorder<br>● Women during breast-feeding or pregnancy |
| Withdraw criteria | ● Patients intraoperatively/postoperatively confirmed as T4b<br>● M1 tumor confirmed intraoperatively or postoperatively: distant metastasis only found by intraoperative exploration or postoperative pathological biopsy or a positive postoperative peritoneal lavage cytology examination<br>● Requirement of simultaneous surgery for other diseas<br>● Patients 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<br>● 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<br>● Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study<br>● Treatment implemented is proven to violate study protocol |

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| ` Outcome Measures | **Primary Outcome Measures**:<br>● Overall postoperative morbidity rates<br>**Secondary Outcome Measures**:<br>● Intraoperative morbidity rate<br>● Operative time<br>● Estimated blood loss<br>● Number of harvested and metastatic lymph nodes<br>● the lengths of incision, proximal and distal margins<br>● Time to first flatus<br>● Time to first liquid diet<br>● Postoperative hospital stay<br>● Total cost |
| Statistical considerations | All data analyses will be performed using SPSS statistical software, version 23.0 (SPSS Inc), and the R software environment (R Foundation for Statistical Computing).<br>All data analyses will be conducted on a per-protocol (PP) basis. This study does not fill in missing values. 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 $\chi 2$ test or the Fisher exact test, as appropriate. Sensitivity analysis is used for extreme outlier data. The confidence interval of the parameters is estimated with a 95% confidence interval. The central effect analysis and subgroup analysis are conducted according to the specific situation. All the statistical tests were tested by two sides. A p-value $<0.05$ is considered statistically significant. |

# 1. Research background

Gastric cancer is a common malignant tumor, and its incidence and mortality are second only to lung cancer. According to estimates by National Cancer Registry of China, there were about 4.29 million new cancer patients and 2.81 million cancer deaths in China in 2015, of which 679,000 new gastric cancer patients and 498,000 gastric cancer deaths were reported[1]. About 90% of patients in China have advanced gastric cancer at the time of diagnosis. According to statistics, 65% of patients with advanced gastric cancer who have a T stage reaching T3 or T4, and as many as 85% of patients with lymph node metastases occur. Without surgical intervention, the median survival time for advanced gastric cancer is only 5.4 months[2]. Although many advances have been made in treatment, radical surgery is still the main treatment method for the gastric. In recent years, with changes in dietary habits and other factors, the incidence of proximal gastric cancer and esophagogastric junction carcinoma has gradually increased[3, 4]. According to UICC, AJCC, JGCA and the consensus and treatment guidelines of Chinese experts, total gastrectomy with D2 lymphadenectomy has become the standard operation for upper gastric cancer and esophagogastric junction carcinoma[5].

Since Kitano first reported the feasibility and safety of laparoscopic radical gastrectomy, laparoscopic radical gastrectomy has been widely carried out. At present, the multi-center prospective randomized controlled study with large-sample has confirmed that early gastric cancer of laparoscopic radical gastrectomy is safe and feasible. It can achieve the effect of radical tumor resection. The long-term follow-up results show that its clinical efficacy is comparable to that of traditional open surgery, and it has significant minimally invasive advantages. Laparoscopic radical gastrectomy for early gastric cancer has become a recommended treatment guideline[5].A multi-center prospective study on distal subtotal gastrectomy for advanced gastric cancer shows that laparoscopic D2 radical distal gastrectomy is safe and feasible[6, 7]. The current research on laparoscopic D2 radical total gastrectomy shows that laparoscopic D2 radical total gastrectomy is safe and feasible, and the long-term effect is comparable to that of laparotomy. Haverkamp et al. [8] meta-analysis that included 314 cases of laparoscopy

and 384 cases of open total gastrectomy showed that although laparoscopy had longer operation time, it could significantly reduce intraoperative blood loss and postoperative complication rate and significantly shorten the length of hospital stay. Etoh et al.[9] conducted a propensity matching analysis of 2494 cases of laparoscopic and open total gastrectomy patients who were registered online in Japan during 2014-2015, and found that there was no statistical difference in surgical complications, including anastomotic fistula and pancreatic fistula, and there was no difference in early postoperative mortality, reoperation rate and readmission rate between the two groups. However, the laparoscopic group had significantly less intraoperative bleeding, more lymph node dissection, and shorter postoperative hospital stay.Hu Jiankun et al. [10] retrospectively analyzed 69 patients and 268 patients who underwent laparoscopic and open D2 radical total gastrectomy from 2006 to 2015, respectively. There were no significant differences between the two groups in terms of total lymph node dissection, blood loss, postoperative hospitalization days, and early postoperative complications, and there were no significant differences in 3-year and 5-year postoperative survival rates between the two groups. We analyzed retrospectively 234 patients with D2 radical total gastrectomy during 2004-2010 with PSM, the number of the lymph node and length of margins in the two groups of patients and there were no significant differences, in terms of intraoperative blood loss, postoperative hospitalization days and postoperative pain, laparoscopic group were significantly better than the open group, The incidence of early postoperative complications was also lower than that of open surgery, and the overall five-year survival rate of the two groups was similar[11].

However, traditional laparoscopic surgery has some limitations, such as limited mobility of laparoscopic instruments, limited field of view, and the two-dimensional plane, lack of three-dimensionality. Due to the complex anatomical structure of the surrounding gastric vessels and the close proximity of blood vessels, it is easy to cause intraoperative bleeding during the lymph node dissection. Moreover, the operation time is long and the learning curve is also long. Especially for patients with obesity, large anteroposterior diameter, and small rib arch angle, the difficulty will be greater, because the deep and narrow abdominal space will seriously affect the laparoscopic surgery.

In 2000, robotic-assisted surgery began to be used in clinical practice. Due to the 3D high-definition images, the elimination of tremor and the flexibility of operation, robotic-assisted surgery has gradually become a frontier and research hotspot in the field of minimally invasive surgery[12].In 2003, In 2003, Hashizume was the first to report the robotic-assisted radical gastrectomy. Since then, many studies and meta-analyses have confirmed that robot-assisted radical gastrectomy can achieve the same short-term and long-term clinical efficacy as laparoscopy[13-15]. However, at present, most studies on robotic-assisted gastric surgery are on distal gastric cancer, and there are few reports comparing robotic and laparoscopic total gastrectomy. Yoon et al. [16] retrospectively analyzed 36 patients and 65 patients who underwent robotic and laparoscopic total gastrectomy from 2009 to 2011. There are no significant differences between the two groups in terms of intraoperative blood loss, postoperative hospitalization days, postoperative complications, and the total number of lymph node dissection. However, the study has a certain limition. These lymph node dissection method are not completely D2 radical resection. Meanwhile，the proportion of patients with early gastric cancer reached 70%. Son et al. [17] retrospectively analyzed 51 patients and 58 patients who underwent total gastrectomy with robotic and laparoscopic splene-preserving D2 during 2003-2010. The operative time of robotic-assisted surgery group was longer than that of the laparoscopic group, and there were no significant differences between the two groups in intraoperative blood loss, postoperative hospital stay, postoperative first flatus and intake time, postoperative complications, and the total number of lymph node dissection, but more lymph node dissection was performed by the robot at 10 and 11p than by the laparoscope (3.6vs1.9;P =0.014). Meanwhile，there was no significant difference in the 5-year overall survival rate and disease-free survival rate between the two groups, but 70% of the cases were early gastric cancer. The above-mentioned literatures suggests that robotic versus laparoscopic total gastrectomy is safe and feasible, but the number of reported cases is small, and most of them are patients with early gastric cancer. In China, 90% of patients are diagnosed with advanced gastric cancer, and total gastrectomy for advanced gastric cancer is more difficult and has a wider range of lymph node dissection. Therefore, it is more necessary

to conduct clinical research on robotic-assisted radical gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer. At present, there is no prospective study report on the treatment of locally advanced gastric cancer with robot and laparoscopic D2 lymph node dissection.

Our center reported the first robotic-assisted gastrectomy in China in 2010, and has completed more than 600 cases of robotic-assisted gastrectomy. At present, there is a lack of prospective research literature reports on robot and laparoscopic radical total gastrectomy combined with D2 lymphadenectomy in the treatment of locally advanced gastric cancer, and the safety and effectiveness of robotic and laparoscopic radical total gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer are still unclear. This study intends to conduct the first international prospective study of robot and laparoscopic radical total gastrectomy with D2 lymphadenectomy for the treatment of locally advanced gastric cancer, and to provide evidence-based medicine for the widespread development of robot-assisted total gastrectomy for locally advanced gastric cancer.

## 2. Objective

The purpose of the prospective trial is to investigate the safety and feasibility between Robotic and laparoscopic radical total gastrectomy with D2 lymphadenectomy for locally advanced gastric cancer.

## 3. Research design

prospective, single-center, non-randomized, controlled, non-blind, and non-inferiority observation trial

### 3.1 Single center

Department of General Surgery and Center of Microinvasive Gastrointestinal Surgery, Southwest Hospital, China

### 3.2 Case group

Group A (Experimental): Robotic-assisted Total Gastrectomy with D2 Lymphadenectomy

Group B（Compared): Laparoscopic-assisted Total Gastrectomy with D2 Lymphadenectomy

### 3.3 Estimate sample size

This study is a non-inferiority study, with postoperative complications as primary outcome. According to the relevant studies, the postoperative complication rate of laparoscopic total gastric surgery is about 15%.In this study, it was assumed that the

postoperative complication rate of the study group was similar to the control group, with α=0.05, β=0.2, and the non-inferiority threshold value set as 15%. PASS 11 was used for calculation, and the sample size of each group was 68 cases. Considering that the maximum detachment rate of this clinical study was 10%, the final sample size was 75 cases in each group.

**3.4 Blind method：** This research adopts an open design

**3.5 Research cycle**

Estimated enrollment cycle: complete enrollment within 3 years

Follow-up period: begin at the enrollment of the first case and end 1 month after the enrollment of the last case.

Estimated time: 2018.01.08-2021.01.08(to complete enrollment)- 2021.02.08(to complete follow-up)

# 4. Study objects

All patients who meet the inclusion criteria and not conform to the exclusion criteria are qualified for this study.

**4.1 Inclusion criteria**

(1) Age between 18 and 80 years

(2) Endoscopic biopsy and CT confirmed locally advanced gastric adenocarcinoma, requiring D2 radical gastrectomy.

(3) Preoperative examination showed no absolute contraindication and no distant metastasis

(4) Performance status of 0 or 1 on ECOG scale

(5) ASA class I, II, or III

(6) Written informed consent

**4.2 Exclusion criteria**

(7) Enlarged or bulky regional lymph node (diameter over 3cm) supported by preoperative imaging including those surrounding important vessels

(8) Emergency surgery due to complication (bleeding, obstruction or perforation) caused by gastric cancer

(9) Previous upper abdominal surgery(except laparoscopic cholecystectomy)

(10) Previous neoadjuvant chemotherapy or radiotherapy

(11) Unstable myocardial infarction, angina, or cerebrovascular accident within the past 6 months

(12) FEV1＜50% of predicted values

(13) Other malignant diseases

(14) Severe mental disorder

(15) Women during breast-feeding or pregnancy

**4.3 Withdraw criteria**

(16) Patients intraoperatively/postoperatively confirmed as T4b

(17) M1 tumor confirmed intraoperatively or postoperatively: distant metastasis only found by intraoperative exploration or postoperative pathological biopsy or a positive postoperative peritoneal lavage cytology examination

(18) Requirement of simultaneous surgery for other diseas

(19) Patients 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

(20) 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

(21) Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study

(22) Treatment implemented is proven to violate study protocol.

# 5. Outcome Measures

**5.1 Primary Outcome Measures**

- Overall postoperative morbidity rates

**5.2 Secondary Outcome Measures**

- Intraoperative morbidity rate
- Operative time
- Estimated blood loss
- Number of harvested and metastatic lymph nodes
- the lengths of incision, proximal and distal margins
- Time to first flatus
- Time to first liquid diet
- Postoperative hospital stay
- Total cost

# 6. Diagnostic criteria for this study

(1) The AJCC-8th TNM tumor staging system will be used for this study.

(2) Diagnostic criteria and classification of gastric cancer: According to the histopathological international diagnostic criteria, classification will be divided into

papillary adenocarcinoma (pap), tubular adenocarcinoma (tub), mucinous adenocarcinoma (muc), signet ring cell carcinoma (sig), and poorly differentiated adenocarcinoma (por).

(3) Definition of advanced stage: tumor infiltration of the stomach wall reaches or exceeds the inherent muscular layer (T2); T2, T3, and T4a patients will be included as study subjects, whereas T4b patients will not.

(4) Definition of esophagogastric junction carcinoma: According to the AJCC-8th tumor staging system, esophagogastric junction carcinoma is defined as a tumor whose tumor center is located within 5cm above and below the esophagogastric junction. According to Siewert classification, the tumor was divided into Siewert type I : the tumor center was located 1 ~ 5 cm above the esophagogastric boundary; Siewert type II : The center of the tumor was 1 cm to 2 cm above the esophagogastric boundary.Siewert type III : The tumor center is located 2 to 5 cm below the esophagogastric boundary. Only Siewert type III esophagogastric junction carcinoma were involved in this study.

# 7 Qualifications of the participated Surgeons

## 7.1 Basic principle

All candidate surgeons in this study met the following criteria:

(1) Performed at least 30 robotic radical total gastrectomies.

(2) Performed at least 50 laparoscopic radical total gastrectomies.

# 8. End point and definition of related result determination

## 8.1 Incidence of operative complications

The number of all patients treated with surgery as the denominator and the number of the patients with any intraoperative and postoperative complications as the numerator are used to calculate the proportions. The criteria for the intraoperative complications refer to the descriptions of intraoperative complications in the observation project (in 9.3.3).

**8.1.1 Incidence of intraoperative complications**

With the number of patients undergoing surgery as the denominator, the number of patients with any of the following intraoperative complications is calculated as numerator. Intraoperative complications are based on the intraoperative complications mentioned in the intraoperative observations.

**8.1.2 Incidence of postoperative complications**

The number of all patients treated with surgery as the denominator and the number of the patients with any intraoperative and postoperative complications as the numerator are used to calculate the proportions.

**8.1.3 Incidence of overall postoperative complications:** The postoperative complication criteria refer to short-term complications after surgery in the postoperative observation project. The time is defined as within 30th after surgery, or the first discharge time if the days of hospital stay more than 30 days.

**8.1.4 Incidence of postoperative major complications:** The standard for postoperative major complications refers to the short-term complications in the postoperative observation project. according to the Clavien–dindo grade, IIIA level and above for serious complications, and when multiple complications occur simultaneously, the highest ranked complication is the subject.

**8.2 Mortality**

- The number of all the patients receiving surgery as the denominator and the number of the patients in any of the following situations as the numerator are used to calculate proportions. This proportion indicated the operative mortality ratio.
- Situations: patients whose death was identified according to documented intraoperative observation items, including patients who die within 30 days after the surgery (including 30 days) regardless of the causality between the death and the surgery, and patients who die more than 30 days after the surgery (whose death is proved to have a direct causal relationship with the first operation).

**8.3 Determination of surgical outcomes**

**8.3.1 Operative time:** from skin incision to the skin being sutured

**8.3.2 Postoperative recovery indexes**

**8.3.2.1 Time to ambulation, flatus, recovery of liquid diet and semi-liquid diet.**

- During the day of surgery to the first discharge, the initial time to ambulation, flatus, liquid diet and semi-liquid diet during the postoperative hospitalization is recorded by

hour.

- Flatus on the operation day should be excluded.
- If flatus or resumption of liquid and semi-liquid diet does not occur before hospital discharge, the discharge time should be recorded as the corresponding time.
- The initial time to ambulation, flatus, liquid diet and semi-liquid diet should be recorded according to patients' reports.

#### 8.3.2.2 Lymph node metastasis

- The number of lymph nodes in each group was used as the denominator, the number of lymph nodes in the final pathological report was used as the molecule, and the proportion of lymph node metastasis in each group was obtained. The proportion of total gastric lymph node metastasis was calculated

# 9 Standard operating procedures (SOP)

## 9.1 Case selection

### 9.1.1 Selection assessment items

Clinical examination data of patients conducted from hospital admission to enrollment into

this study (time period is usually 2 weeks) will be considered baseline data, and must include:

(1) Systemic status: ECOG score, height, weight, BMI, ASA score;

(2) Peripheral venous blood: Hb、RBC、WBC、LYM、NEU、NEU%、PLT、MONO

(3) Blood biochemistry: albumin, prealbumin, total bilirubin, indirect bilirubin, direct bilirubin, AST, ALT, creatinine, urea nitrogen, Total cholesterol, triglycerides, fasting glucose, potassium, sodium, chlorine, calcium

(4) Serum tumor markers: CEA、CA19-9、CA72-4、CA12-5、AFP

(5) Full abdominal (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(Chest CT replacement is permitted)

(8) Resting 12-lead ECG

(9) Respiratory function tests: FEV1, FVC

**9.1.2 Selection application**

For cases that meet all inclusion criteria and none of the exclusion criteria, talk to patients and their families and sign informed consent. Application and confirmation of eligibility should be completed preoperatively; postoperative applications will not be accepted.

**9.2 Preoperative management**

- 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 Withdrawal Criteria;
- 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 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 can decide on the most appropriate approach according to clinical practice and should record it in the CRF.
- For the operative approach of the surgeries in this study 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, which is not specified in this study.
- For prophylactic antibiotics, the first intravenous infusion should begin 30 minutes before 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 24 hours (special case can be extended to 48 hours) at a frequency of one infusion every 12 hours. If a patient is allergic to

cephalosporins (including the 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 period mentioned.

### 9.3 Standardization of surgical practice

#### 9.3.1 Principle of Surgical Treatments

##### 9.3.1.1 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.

##### 9.3.1.2 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.

##### 9.3.1.3 Intraoperative exploration

Explore the abdominal cavity for any hepatic, peritoneal, mesenteric, or pelvic metastases and gastric serosal invasion

##### 9.3.1.4 Regulations on the extent of the gastrectomy

Follow the Japanese gastric cancer treatment guidelines 2014 (ver. 4) to perform total gastrectomy under the premise of satisfying the oncological principles.

##### 9.3.1.5 Regulations on the extent of the Lymph node dissection

Follow the Japanese gastric cancer treatment guidelines 2014 (ver. 4): Total gastric resection with D2 Lymphadenectomy (No. 1,2,3,4,5,6,7,8a,9,10,11,12a).

##### 9.3.1.6 Regulations Regarding Greater Omentum Resection

This study protocol requires total greater omentum resection.

##### 9.3.1.7 Regulations Regarding Digestive Tract Reconstruction

The digestive tract reconstruction method is determined by the surgeon according to his/her own experience and the specific intraoperative situation. If instrumental anastomosis is used, the surgeon determines whether manual reinforced stitching of the anastomotic stoma is to be performed; the study protocol does not specify.

#### 9.3.1.8 Regulations Regarding Surgery-related Equipment and Instruments

The energy equipment, vascular ligation method, digestive tract cutting closure, and digestive tract reconstruction instruments are determined by the surgeon responsible for surgery based on experience and actual needs and are not specified in this study protocol.

#### 9.3.1.9 Regulations Regarding Gastric Canal and Peritoneal Drainage Tube

Whether the gastric canal or peritoneal drainage tube is left after surgery is determined by experience and actual needs and is not specified in this study protocol,and record the reasons in the CRF.

#### 9.3.1.10 Regulations Regarding Concurrent Surgical Treatments

If another organ/system disease is present, the responsible surgeon and the relevant department consultants will jointly decide whether a concurrent operation is required and can be performed. The order is determined according to the clinical routine, but these cases will be excluded from the PP set according to the Exclusion Criteria.

#### 9.3.1.11 Regulations Regarding the Processing of Excluded Patients Identified Intraoperatively

If the patient is judged to meet the exclusion requirements during the operation, the study approach will be suspended, and the responsible surgeon will decide upon the subsequent treatment according to the clinical practice of the research center (the therapeutic decision, such as whether to excise the gastric primary focus or metastases, is determined by the responsible surgeon). These cases will be excluded from the PP set according to the Exclusion Criteria.

#### 9.3.1.12 Regulations on conversion to laparotomy

When intra-abdominal hemorrhage, organ damage and other serious/life-threatening complications which are difficult to control occur during robotic 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 open. The surgeon in charge can decide to convert to laparotomy driven by other technical or equipment reasons and will record said reasons. The reasons for the conversion to open must be clearly recorded in the CRF. The incision length of > 10 cm is defined as a case of

conversion to open surgery in this study.

### 9.3.2 Operative parameters (same for both groups)

Completed by the research assistant on the day of the operation. specific projects include:

(1) Name of responsible surgeons

(2) Operation time (min)

(3) Type of operation, digestive tract reconstruction, intraoperative damage and whether the tumor was ruptured during surgery (intact rupture of the capsule)

(4) Length of incision (cm)

(5) Conversion to open surgery or not and the reasons for this decision

(6) Intraoperative estimated blood loss (ml; from skin cutting to stitching, intraoperative blood loss = (postoperative gauze weight, grams - preoperative gauze weight, grams) *1ml/g+ suction fluid, ml)

(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 location

(9) Tumor size (maximum tumor diameter, mm)

(10) Number of lymph nodes dissected in each group and distant metastasis (location)

(11) Proximal resected margin (mm), distal resected margin (mm), radicality(R0/R1/R2)

(12) Intraoperative complications (occurring from skin incision to skin closure) including:

surgery-related complications: intraoperative hemorrhage and injury: A. Vascular injury: A vascular injury is defined as a blood vessel with either a blood vessel clamp or a titanium clamp closure and an intra-cavity suture or any other method to control the bleeding. B. Organ damage: maybe including diaphragmatic injury, esophageal injury, duodenal injury, colon injury, small intestine injury, spleen injury (excluding <1/3 spleen ischemia), liver injury, pancreatic injury, gallbladder injury, kidney damage etc.

C. Tumor rupture: tumor envelope Integrity damage

air abdominal-related complications: high-blood carbonate, mediastinal emphysema, subcutaneous emphysema, air embolism, respiratory circulation instability caused by abdominal pressure.

Anesthesia-related complications: Allergic reactions.

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

### 9.3.3 Postoperative management

#### 9.3.3.1 The use of prophylactic 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

#### 9.3.3.2 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.

#### 9.3.3.3 Post-operative 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.

#### 9.3.3.4 Discharge standard

Patients needed to meet the following criteria for discharge: 1) satisfactory intake of a soft diet. 2) move around of their bed. and 3) absence of complications by routine clinical examinations. This information will be recorded in the CRF.

### 9.3.4 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:

(1) Pathologic results：

Original lesion tissue typing, Distant metastasis, and parts, NIH Hazard grading, Radical surgery degree (R0/R1/R2), The total number of lymph nodes, the number of lymph nodes in each group, the number of lymph node metastases in each group and the total number of metastases in pathological specimens were obtained

(2) Postoperative complications：

Postoperative complications are divided into and short-term complications after surgery and long-term complications after surgery. Short-term is defined as within 30 days of surgery or the first discharge if the hospital days > 30 days. Long-term is defined as the period from 30 days or more after the operation, or the first discharge (the hospital days after surgery >30 days) to 3 years after the operation.

**Severity of complication is graded according to Clavien–dindo complication scoring system, [19]**

**IIIA level and above are serious complication**

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

II：Requiring pharmacologic treatment with drugs other than such allowed for

grade I complications. Blood transfusions and total parenteral nutrition are also included.

III：Requiring surgical, endoscopic, or radiologic intervention

IIIa：Intervention not under general anesthesia

IIIb：Intervention under general anesthesia

IV： Life-threatening complication (including CNS complications) requiring IC(intermediate care)/ICU(intensive care unit)

management

IVa：Single organ dysfunction (including dialysis)

IVb：Multiple organ dysfunction

V：Death as a result of complications

| Classification and name of complication | Diagnostic criteria |
|---|---|
| Abdominal bleeding | Intra-abdominal hemorrhage requires blood transfusion, emergency endoscopy or surgical intervention to eliminate anastomotic bleeding |
| Anastomotic bleeding | The postoperative gastrointestinal decompression tube continued to have fresh red blood outflow; the hemoglobin drops more than 1g/dL |
| Gastrointestinal anastomotic stoma Fistula | Using gastrointestinal angiography to see contrast agent leak out from the anastomosis, or the blue drainage outflow through tube after oral Methylene blue to eliminate the possibility duodenal stump fistula and |

| | |
|---|---|
| | intestinal fistula |
| Duodenal Stump Fistula | Using gastrointestinal angiography to see contrast agent leak out from the duodenal stump to eliminate the anastomotic fistula or intestinal fistula |
| Intestinal fistula | Using gastrointestinal angiography to see the blue drainage outflow through tube after oral Methylene blue to eliminate anastomotic fistula and duodenal stump fistula |
| Stenosis of Anastomosis | Endoscopic examination with a 9.2-mm endoscopy not passing through the anastomosis to eliminate recurrence of tumors |
| Input jejunal loop obstruction | Abdominal pain, abdominal distension, vomiting and other symptoms. Abdominal flat to see the right upper abdomen expansion of the intestinal loop, and there is a liquid plane, or a visible input loop jejunum giant expansion by barium meal examination. |
| Intestinal obstruction after operation | Abdominal X-ray shows a plurality of liquid planes and the phenomenon of intestinal effusion with visible isolated, fixed, swelling of the intestinal loop. Total Abdominal CT showed edema, thickening, adhesion of intestinal wall, accumulation of gas in intestinal cavity, uniform expansion of bowel and intra-abdominal exudation. |
| Early dumping syndrome | Combined the symptoms of sweating, heat, weakness, dizziness, palpitations, heart swelling feeling, vomiting, abdominal colic or diarrhea with the signs of tachycardia, blood pressure micro-rise, breathing a little faster sign after meal 15-30 minutes, and solid phase radionuclide gastric emptying scanning tips stomach quickly emptying. |
| Late dumping syndrome | Feeling hungry, flustered, out of sweating 2-3 hours after the meal . Blood sugar is less than 2.9mmol/L, excluding other diseases that cause hypoglycemia |
| Intestinal ischemia and necrosis | Under the digestive endoscopy, the intestinal mucosa congestion, edema, bruising, mucosal hemorrhage, the mucous membrane being dark red, the vascular network disappearing, can have part mucosal necrosis, following with mucosal shedding, ulcer formation with annular, longitudinal, snake and scattered in the ulcer erosion. |
| Internal hernia | Postoperative CT findings of cystic or cystic and solid mass, and intestinal aggregation, stretching, translocation, abnormal mesenteric movement, and thickening of the blood vessel. |
| Alkaline reflux esophagitis | 1. Endoscopic examination and biopsy of the upper gastrointestinal |

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| | tract showed evidence of inflammation of the mucous membranes and gastrointestinal metaplasia; 2. CT scan and gastrointestinal barium meal examination showed no expansion or obstruction of the input loop. |
| Incision splitting | Including partial dehiscence of the incision and full-layer dehiscence |
| Incisional hernia of abdominal wall | The swelling tumor showing in the surgical scar area or abdominal wall swelling when standing or force. CT shows ventral wall continuity interruption and hernia content extravasation |
| Incision infection | Thickening of the soft tissue at the incision, in or below the incision of gas, exudation, swelling of the incision or pus from the incision extrusion, or secretion culture of pathogenic bacteria. |
| Lymphatic leakage | A chyle test when abdominal drainage fluid exceeded 300 ml/day for 5 consecutive days after postoperative day 3. |
| Pneumonia | Complies with one of the following two diagnostic Criteria: 1. Auscultation/percussion voiced + one of the following: fresh sputum or sputum character changes; blood culture (+); bronchoalveolar lavage fluid, anti-pollution sample brush, biopsy specimens cultured pathogenic bacteria. 2. Chest film hints of new or progressive infiltration + one of the following: fresh sputum or sputum character changes, blood culture (+), bronchoalveolar lavage fluid, anti-pollution sample brush, biopsy specimens cultured pathogenic bacteria; isolate virus or detect IgM, IgG (+) of respiratory viral |
| Acute pancreatitis | Irritability, abdominal pain, anti-jumping pain, fever, leukocyte increase and blood amylase increased occuring and diagnosed by ultrasound or CT within 3 days after surgery. |
| Acute cholecystitis | Serum bilirubin exceeding 85μmol/l and ultrsound examination shows gallbladder enlargement, wall thickness, signal and sound shadow of gallbladder stone, bile internal sediment, gallbladder contraction bad etc. |
| Pleural effusion/infection | CT scan showed the localized fluid low density area of thoracic cavity, which could accompany with gas, and culture pathogenic bacteria in thoracic endocrine. |
| Abdominal infection | There is at least one of the following evidences in abdominal cavity within 30 days after operation: 1. discharge of pus, with/without microbiological examination; 2. bacterial culture positive; 3. diagnosed by detection, pathology, imaging findings. |

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| Pelvic infection | Symptoms of systemic infection or rectal irritation, combined with a rectal finger examination and touching tenderness, or a married woman with a posterior vault to extract pus-based fluid |
| Sepsis | The following two conditions are available: 1. There is evidence of active bacterial infection, but the blood culture does not necessarily appear pathogenic bacteria; 2. meeting two of the following four items at the same time: (1). body temperature >39. 0℃ or < 35.5 ℃ for 3 consecutive days, (2). heart rate > 120 times/min; (3). total white blood cells >12. $0*10^9$/L or <4.$0*10^9$/l, wherein neutrophils >0. 80, or naïve granular cells >0. 10; (4).Respiratory frequency > 28 times/min |
| Urinary system infection | Symptoms of urine frequency, urgency and urine pain etc. and urine bacteria culture colony count 1000~10 million/ml in the absence of antibiotics; No symptoms of urine frequency, urgency and urine pain etc, urine bacterial culture colony count ≥ 100,000/ml |
| Pancreatic fistula | The level of amylase in the drainage fluid is three times than normal level. |
| Bile fistula | Symptoms of abdominal distension, Abdominal pain, tenderness, anti-jumping pain, muscle tension, abdominal puncture or drainage fluid for bile |
| Celiac fistula | The drainage fluid is milky white, and more than 200ml/d and and does not decrease for 48 hour, the celiac qualitative test is positive, and the level of triglyceride >110 mg/dL at the same time. |
| Nutritional disorder after gastrectomy | In the presence of weight loss, anemia, malnutrition bone disease, vitamin A deficiency and other symptoms, laboratory tests suggest that the intestinal absorption function test is abnormal, excluding other causes of nutritional disorders |
| Bone disease after gastrectomy | Lumbar back pain, length shortening, kyphosis, bone fractures and other symptoms. Bone density decreased combining with elevated alkaline phosphatase and serum calcium reduction, the concentration of serum 25-(O1) D3 and 1,25-(O1) 2D3 increasing and the serum parathyroid hormone increasing. Exclusion of bone disease caused by other causes. |
| Subcutaneous emphysema | visible the irregular speckle shadow under the skin in the horizontal flat sheet. |
| Mediastinal emphysema | In the posterior and anterior flat fame, a long narrow gas shadow rises to the neck soft tissue along the mediastinal side, forming a thin-line |

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| | dense shadow. In the lateral flat there was a visible and clear band between the heart and the sternum. The CT examination, if necessary, shows gas density line-like shadow around the mediastinal and mediastinal pleura closing to the direction of the lung field. |
| Postoperative hemorrhage | An amount of hemorrhage exceeding 300 ml. |
| Postoperative cardiac dysfunction | The symptom of snus tachycardia, sinus bradycardia, supraventricular tachycardia, ventricular tachycardia, and other arrhythmias, or heart failure preoperatively none-existing and postoperatively appearing,.and other causes of the above-mentioned manifestations are excluded. |
| Hepatic dysfunction | Bilirubin increasing and the levels of AST and ALT >5 times after operation and these symptoms no existing before sugery, |
| Kidney function failure | Postoperative continuing renal function insufficiency, blood creatinine rising 2mg/dl, or acute renal failure needing dialysis treatment. |
| Cerebral embolism | Acute onset, hemiplegia, aphasia and other focal neurological function deficits. Embolism site has low-density infarction, of which border is not clear and no obstructional performance within 24-48 hours after the onset. |
| Pulmonary embolism | Characteristics of dyspnea, chest pain, syncope, shortness of breath, right ventricular insufficiency and hypotension, pulmonary angiography revealed a filling defect. |
| Venous thrombosis of lower extremities | Local tenderness, swelling, purple skin color, combined with intravenous angiography to show the filling defect |
| Mesenteric arterial embolization | Patients with acute abdominal pain, vomiting, diarrhea, abdominal x-ray of intestinal tract filling with gas or existing liquid level, abdominal angiography revealed a filling defect. |
| DIC | 1.There are basic diseases easily leading to DIC, 2. There are more than two clinical performances: (1) severe or multiple bleeding tendencies; (2) Microcirculation disorder or shock cannot be explained by the original disease. (3) Extensive skin mucosal embolism, focal ischemic necrosis, shedding and ulcer formation, or unexplained lung, kidney, brain and another organ failure. (4) anticoagulant treatment.is effective. 3. The laboratory meets the following conditions: (1) there are 3 or more experimental abnormalities: platelet count, prothrombin time, activated partial coagulation enzyme time, thrombin time, fibrinogen level, D-two poly, and (2) difficult or special cases for special examination. |

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| Other | Complications other than the above complications, which do not exist before surgery but appear after surgery |

(1) Blood test items (At postoperative day 1, 3, 5)

Peripheral blood routine assessment: Hb, RBC, WBC, LYM, NEU, NEU%, and PLT、MONO；

Blood biochemistry: Albumin, prealbumin, total bilirubin, AST, ALT, creatinine, urea nitrogen, fasting blood glucose, potassium, sodium, chlorine, calcium, CRP, IL-6, PCT, Blood amylase, ascites amylase.

(2) Postoperative rehabilitation evaluation：

Time to first ambulation (hours), time to first flatus (hour), time to liquid diet, time to removal of gastric tube (d), daily volume of gastric drainage (ml), time to removal of abdominal drainage tube (d), daily volume of drainage (ml).Blood transfusion volume (ml) from the end of surgery to postoperative discharge: a transfusion event is defined as infusion of the red blood cell suspension (ml) or whole blood (ml).Postoperative hospital stays (days): periods form surgery day to first discharge day

**9.4 Follow-Up**

**9.4.1 Follow-up Period and strategy**

Follow-up visits will be completed by special persons for all cases selected in this study .All patients are followed up with 30 days, Recommend patient follow-up every 3 months during the first 2 years and then every 6 months beyond the third year (1、 3、 6、 9、 12、 15、18、21、24、30 and 36 months after the operation),and record with patients' consent. This study suggests that the above examinations should be conducted in the patient's primary surgical research center, but does not exclude outer court review. For Outer Court review, It recommended that visiting the hospital as a three-level hospital, and these information will be recorded by the follow-up specialist. The occurrence of tumor recurrence or metastasis and the survival status of all patients are evaluated and recorded according to the results of the various examinations. Patients who refuse to follow the protocol should be recorded as lost to follow-up, and at the end of the study, these cases should be analyzed together with cases lost to follow-up in line with the criteria of this study.

### 9.4.2 Assessment items during the 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. Meanwhile, ask about general conditions (Height, weight, BMI, diet).

(2) Blood test items:

Peripheral blood routine assessment: Hb、RBC、WBC、LYM、NEU、NEU%、PLT、MONO

Biochemistry: Albumin, pre-albumin, total bilirubin, Indirect bilirubin, direct bilirubin, AST, ALT, creatinine, urea nitrogen, Total cholesterol, triglycerides, fasting blood glucose, potassium, sodium, chlorine, calcium, serum tumor markers: CEA 、CA19-9、CA72-4、CA12-5、AFP.

(3) Imaging items:

Recommend patient take imaging examination every 3 months during the first 2 years and then every 6 months beyond the third year (1、 3、 6、 9、 12、 15、18、21、24、30 and 36 months after the operation). Including: 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.

## 9.5 Post-operative adjuvant therapy

### 9.5.1 Indications for postoperative adjuvant chemotherapy

After completion of the surgical treatment, according to the postoperative pathological results, subjects among the R0 resection cases that are stage II and above are administered postoperative adjuvant chemotherapy according to the provisions of this program.

For cases of non-R0 resection or recurrence after R0 resection, this study does not

stipulate the follow-up treatment plan; the research center decides on the action to be taken according to the clinical treatment routine.

**9.5.2 Postoperative adjuvant chemotherapy**

This study uses a combination of chemotherapy based on 5-FU (5-fluorouracil) and recommends the SOX regimen.

In cases of good physical and tolerable conditions, chemotherapy is first started within 3-4 weeks after surgery and then according to the regularity of the chemotherapy cycle.

During the chemotherapy period, tumor recurrence should be assessed according to the follow-up plan.

When tumor recurrence occurs during chemotherapy, the adjuvant chemotherapy regimen of this study is discontinued. The follow-up treatment is decided by the research center according to the clinical treatment routine. This study does not make regulations, but the cause and follow-up treatment plan should be recorded in the CRF.

Adjuvant chemotherapy requires written approval from the patient.

Subjects that refuse postoperative adjuvant chemotherapy or do not complete the adjuvant chemotherapy are not excluded from this study, but the cause is marked and recorded in the CRF.

Patients who choose adjuvant chemotherapy, irregular chemotherapy, or a non-first-line regimen are not excluded from the study, but Safety Evaluation Committee is obliged to monitor patient safety during follow-up. The patient's chemotherapy medication must be recorded in the CRF.

### 9.5.3 Safety Evaluation Indicators of Postoperative Adjuvant Chemotherapy

The safety evaluation indicators for 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 the following:

(1) Performance Status (ECOG)

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

(3) Blood tests:

Peripheral venous blood assessment: Hb, RBC, WBC, LYM, NEU, NEU%, PLT, MONO.

Blood biochemistry: albumin, prealbumin, total bilirubin, AST, ALT, creatinine, urea nitrogen, fasting blood glucose, serum tumor markers (CEA, CA19-9, CA72-4, CA12-5, AFP)

(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

# 10 Statistical analysis

## 10.1 Statistical analysis plan

- Statistical software: we will use SPSS statistical software, version 23.0 (SPSS Inc), and the R software environment (R Foundation for Statistical Computing) to perform statistical analyses.
- Basic principle： The method of differential testing was adopted. The safety population of the study consists of the patients who receive safety evaluation data after the intervention. Descriptive statistics and two-sided tests were conducted for the safety indicators and the incidence of adverse reactions. A p-value $<0.05$ is considered statistically significant. The confidence interval of the parameters is estimated with a 95% confidence interval.
- Shedding analysis: Total shedding rate of two groups and loss rate due to adverse events will be compared using pearson$\chi^2$ test

- All data analyses will be conducted on a per-protocol (PP) basis.
- Method of outlier determination: the observation value is greater than P75 or less than P25, and the exceed value more than 3 times of the quartile spacing (=p75-p25), which will be sentenced to outlier data. During the analysis, the sensitivity analysis is used for outlier data, namely analyzing outcomes including or excluding, outlier's data. and if the results are not contradictory, the data is retained; if the contradiction, it depends on the specific circumstances.
- Descriptive statistics: The measurement data gives the mean, the standard deviation and the confidence interval, and the minimum value, the maximum value, the P25, the median and the P75 are given when necessary; matched data also gives the mean and standard deviation of the gap-value, and the median and average rank of the Non-parametric method. The nominal-scale data gives the frequency distribution and the corresponding percentages. The level data gives the frequency distribution and the corresponding percentages, as well as the median and the average rank. Qualitative data give positive rate, positive number, and denominator numbers. The survival data gives the number of events, the number of deletions, the median survival time, and the survival rate.
- Subgroup analysis： Sub-group analysis is to find the factors that may affect prognostic according to the specific circumstances of the data。
- Missing values handling：This study does not fill in missing values
- Safety analysis: counting adverse responds incidence and incidence of adverse events and make a list to describe the adverse events occurring in the study. describe the results of the laboratory tests before and after the normal/abnormal changes and the relationship between the abnormal changes and drugs in the research, and make a list on the "normal/abnormal" changes occurred in the study.. More detailed statistical analysis is shown in the statistical analysis plan.

# 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: 1-7 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 Method of transmission of CRF

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

### 11.1.3 Revision of CRF

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 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.

### 11.2 Monitoring and Supervising

To assess whether study implementation follows protocol and data are being collected properly, monitoring should be conducted every February during the follow-up period. Monitoring is to complete through visiting a hospital and comparing the original Data.

## 12 Relevant Provisions on adverse events

### 12.1 Various forms of adverse events caused by original incidence

Adverse events relating to various forms of deterioration in primary diseases should be recorded according to Short Name of CTCAEv4.0.

### 12.2 Evaluation of adverse events

- Evaluation of adverse event/adverse reaction are based on[Accordion Severity Grading System] and [CTCAE v4.0].
- Adverse events will be graded 1 ~ 5 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 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 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) 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)

**12.3 Reporting of Adverse Events**

- When “severe adverse events” or “unexpected adverse events” occur, the Research Responsible Person of research participating unit should report them to the Research Committee.
- Based on the relevant laws and regulations, adverse events should be reported to the province (city) Health Department at the location of the 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 the 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 emergent reporting objects are.

#### 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 Research Committee by email and telephone.
- Second Reporting: The research responsible person of the 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 Research Committee within 15 days after the occurrence of adverse events. If any autopsy examination, the autopsy result report should be submitted to the Research Committee.

**12.3.2.2 General Reports**

- The research responsible person of research participating hospital completes the "AE/AR/ADR report", and then faxes it to the Research Committee within 15 days after the occurrence of adverse events.

**12.5 Review of Efficacy and Safety Evaluation Committee**

The 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 researchers

The investigators are responsible for the conduction of this study. 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 Supervising

The research approach of the authorities and any associated files (such as the research protocol, subjects' informed consent) will be in accordance with the requirements of the ethical review board of biomedical research involving humans (Trial) (2007) and the applicable Chinese laws and regulations. Studies should provide the main references or inform the ethics review guidance advisory organization of the provincial health administrative department in the province the research center is in.

## 14 Organizations and Responsibilities of Study

### 14.1 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 Research Committee: Peiwu Yu (Department of General Surgery and Center of Microinvasive Gastrointestinal Surgery,Southwest Hospital, China)

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### 14.2 Efficacy and Safety Evaluation Committee

Responsible for the supervision/monitoring of treatment safety and efficacy of this study.

- Person in Charge of Efficacy and Safety Evaluation Committee: Peiwu Yu (Department of General Surgery and Center of Microinvasive Gastrointestinal Surgery,Southwest Hospital, China)

### 14.3 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.

IRB number: KY201810

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# 16.Annex

## 16.1Informed Consent Form

# Informed Consent Informed Notification page

**（Vision：2.0 Date of edition: 2018.01.08）**

**Dear patient：**

You have been diagnosed with_____.We are currently carrying out research and will perform robotic radical gastrectomy or laparoscopic radical: **Safety and feasibility between Robotic and laparoscopic D2 radical total gastrectomy for locally advanced gastric cancer(NCT03500471)**.**Robotic-assisted or laparoscopic gastrectomy** to treat your disease according to your will. The clinical study protocol has been submitted to the Medical Ethics Committee of Southwest Hospital for review and approval.

Before you decide whether or not to participate in this clinical study, please read the following as carefully as possible.It can help you understand the clinical study, why the clinical study was conducted, the procedure and duration of the study.If you wish, you can discuss it with your relatives, friends, or ask your doctor for an explanation to help you make a decision.

**1、Clinical background and purpose**

**1.1 Current status of disease treatment:** Although many advances have been made in treatment, radical surgery is still the main treatment method for the gastric. At present, total gastrectomy with D2 Lymphadenectomy is the standard surgical method for advanced gastric cancer such as upper stomach and esophagogastric junction carcinoma. The surgical methods can be divided into open surgery and minimally invasive surgery. Minimally invasive surgery has the advantages of less trauma, less bleeding, less postoperative pain, faster recovery, less complications and so on. It has been widely used at home and abroad and achieved good clinical results. Minimally invasive surgery includes laparoscopic surgery and robotic surgery.

**1.2 Objective:** In this study, A prospective cohort study was conducted to compare and observe the differences between robotic-assisted radical gastrectomy and laparoscopic surgery for advanced gastric cancer in terms of surgical efficacy and postoperative complications. Therefore, the safety and efficacy of the operation were evaluated scientifically, providing evidence based medicine for its extensive development.

**1.3 Your current treatment options:** Radical gastrectomy is the main method for the treatment of advanced gastric cancer, and the surgery should meet the requirements of D2 radical gastrectomy. At present, the minimally invasive

surgical methods you can choose include robotic-assisted D2 radical gastrectomy and laparoscopic D2 radical gastrectomy.

**2、Who should not participate in a clinical study**

1.Patients with early gastric cancer；

2.Age<18 years or Age>80 years；

3. radical total gastrectomy with D2 Lymphadenectomy is not required；

4..Enlarged or bulky regional lymph node (diameter over 3cm) supported by preoperative imaging including those surrounding important vessels

5.Emergency surgery due to complication (bleeding, obstruction or perforation) caused by gastric cancer

Previous upper abdominal surgery (except laparoscopic cholecystectomy)

6.Previous neoadjuvant chemotherapy or radiotherapy

7.Unstable myocardial infarction, angina, or cerebrovascular accident within the past 6 months

8.FEV1＜50% of predicted values

9.Other malignant diseases

10.Severe mental disorder

11.Women during breast-feeding or pregnancy

**3、What will you do if participate in a clinical study？**

1．A total of 150 people will be included in this study for 3 years. Before you are enrolled in the clinical study, the doctor will ask and record your medical history, and perform blood routine examination, Blood biochemistry, Serum tumor markers, gastroscopy, upper abdominal CT and other examinations. If you meet the inclusion and exclusion criteria, you may voluntarily participate in the clinical study and sign an informed consent form.
If you do not wish to participate in the clinical study, we will treat you as you wish.

2. If you volunteer to participate in the clinical study, you will follow the following steps：

1) You have accepted our initial screening after admission and are a candidate for inclusion in this clinical study. We will inform you and your family members of the details of this clinical study in detail and answer all your questions. Please sign the informed consent for this clinical study after you confirm that you are fully informed of all the contents of this clinical study.

2) At the same time, you will be asked to fill in detailed personal information. We will make every effort to protect the privacy of your personal information within the scope permitted by law.

3) According to the medical operation routine, decide whether to adopt robotic-assisted radical gastrectomy or laparoscopic radical gastrectomy according to your will. You and your family will be informed and signed the informed consent for surgery.

4) After the operation, we will carefully observe and record your recovery, and inform you or your family members of your condition in time. At the same time, we also need your cooperation to complete some necessary examinations.

5) After the operation, we will further determine whether you will receive chemotherapy according to the pathological diagnosis. During this period, we will carefully observe and record your various symptoms and signs, and actively deal with your various post-chemotherapy discomfort.

**6)** Postoperative follow-up plan: The first follow-up will be conducted 1 month after the operation. The follow-up doctor will perform physical examination, and the related laboratory tests mainly include blood routine examination, Blood biochemistry, Serum tumor markers, etc. If necessary, upper abdominal enhanced CT examination, chest X-ray examination, gastroscopy examination, etc. At the same time, the postoperative quality of life was assessed by international standards EORTC QLQ-C30 V 3.0 and EORTC QLQ-STO22.

3. Other matters that require your cooperation

You should go to the hospital according to the appointment of the doctor and you (during the follow-up period, the doctor may call or visit you to learn about your situation).Your follow-up is important because your doctor will determine whether the treatment you are receiving is really working and will guide you in a timely manner.

If you need additional treatment, please contact your doctor.

**4、Possible benefits of participating in this clinical study**

You will not benefit from this study, but the relevant data and information obtained from this study will provide a more reliable evidence-based medical basis for the treatment of delayed gastric cancer with total gastrectomy to benefit future patients.

**5、Possible adverse reactions, risks and inconveniences of participating in this clinical study**

We will enter the robotic or laparoscopic group as you wish.The possible risks, adverse reactions, and various surgical complications of the patients in any surgical group cannot be completely prevented by the current medical level, and we will inform them in detail in the form of surgical informed consent before surgery.

If you experience any discomfort, deterioration of illness, or any unexpected situation during the clinical study, whether related to surgery, you should inform your doctor promptly, who will make a judgment and give appropriate medical attention.

You should go to the hospital on time, which takes up some of your time, but also may cause trouble or inconvenience to you.

**6、Terms for expenses and damages**

**1. expenses**

Both of the two surgical methods are commonly used in clinical practice. Follow-up is also required in routine medical treatment, and the corresponding costs should be borne by you.

The possible cost of laparoscopic surgery is about ¥90,000, and that of robotic surgery is about ¥110,000. If there are complications related to surgery and anesthesia, the treatment costs will increase.

Postoperative follow-up and examination items were all routine items after gastric cancer surgery, and the costs should be paid by the patients themselves.

We will provide you with health consultation related to gastric cancer, physical examination and quality of life evaluation according to the follow-up requirements, and may give you follow-up by phone or letter.

You need to pay for the treatment and examination of other diseases you have combined.

2. **Injury compensation clause**

If there is any damage related to this study, we will compensate in accordance with the relevant requirements of relevant laws and regulations of the people's Republic of China (the operation risk of the two operation methods is not considered as the research risk of this study)。

**7、Is personal information confidential?**

Your medical records (surgical records, examination results, etc.) will be completely kept in the hospital. The doctor will record the test results on your medical record. The surgeon and ethics committee will be allowed to access your medical records. Any public report on the results of this clinical study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data to the extent permitted by law.

**8、How to get more information?**

You can ask any questions about this clinical study at any time and get the corresponding answers.

If there is any important new information during the clinical study that may affect your willingness to continue to participate in the clinical study, your doctor will inform you in time.

If you have any questions about the procedure of this study, you can consult **Dr. Li Pingang** at **(023) 68754167**. If you have any questions about your rights and interests to participate in this study, you can consult **the ethics committee of southwest hospital of China** at **(023) 68754814**.

**9、Voluntarily choose to participate in clinical research and withdraw from clinical research**

Whether to participate in the clinical study depends entirely on your wishes. Participation in this study will not have any therapeutic impact on you. You may refuse to participate in this clinical study or withdraw at any time during the clinical study, which will not affect the relationship between you and the doctor, nor will it affect the loss of your medical treatment or other interests.

For your best interests, the doctor or surgeon may suspend you from continuing to participate in the clinical study at any time during the clinical study.

This test will be aborted or withdrawn if:**：**

1. Patients intraoperatively/postoperatively confirmed as T4b.

2. tumor confirmed intraoperatively or postoperatively: distant metastasis only found by intraoperative exploration or postoperative pathological biopsy or a positive postoperative peritoneal lavage cytology examination.

3.Requirement of simultaneous surgery for other diseas.

4.Patients 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.

5.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.

6.Patients who voluntarily quit or discontinue treatment for personal reasons at any stage after inclusion in this study.

7.Treatment implemented is proven to violate study protocol.

If you withdraw from the clinical study for any reason, you will proceed to the next step under the guidance of your

doctor.

**10、What should you do now?**

Whether to participate in this clinical study is up to you (and your family).

Before you make a decision to participate in the clinical study, please ask your doctor as many questions as possible.

Thank you for reading the above materials. If you decide to participate in this clinical study, please tell your doctor and he / she will arrange all matters related to the clinical study for you. Please keep this information.

# Informed consent· Signature page

**（Date of edition：2018.01.08）**

**Title of clinical study：Safety and feasibility between Robotic and laparoscopic D2 radical total gastrectomy for locally advanced gastric cancer:A prospective cohort study**

## Declaration of consent:

I have read the above introduction about this clinical study, and have the opportunity to discuss and ask questions with doctors about this clinical study. All my questions were answered satisfactorily.

I know the possible risks and benefits of participating in this clinical study. I know that participating in the clinical study is voluntary. I confirm that I have had enough time to consider this and understand that:

I can always ask the doctor for more information.

I can withdraw from this clinical study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also know that if I withdraw from clinical research halfway, I will tell the doctor about the changes of my condition and complete the corresponding physical and chemical examination, which will be very beneficial to the whole condition.

If I need to take any other treatment due to the change of my condition, I will consult the doctor in advance or tell the doctor truthfully afterwards.

I agree with the ethics committee or its representative to access my clinical research data.

I will receive a signed and dated copy of the informed consent form.

Finally, I decided to agree to participate in this clinical study and promise to follow the doctor's advice as much as possible.

**Participant signature：** _____ **Date:** __ __ __ __ __ __ __ __

**Legal representative：** _____ **Date:** __ __ __ __ __ __ __ __

**Relationship with participant：** _____

**Phone number：** _____

I confirm that I have explained the details of this clinical study to the patient, including its rights, possible benefits and risks, and gave him a copy of the signed informed consent form.

**Doctor signature：** _____ **Date:** __ __ __ __ __ __ __ __

**Phone number：** _____

## 16.2Definitions involved in SOP

### 16.2.1 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 housework, 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. In total, 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.

**16.2.2 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):

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

Class II: Patients with mild complications and good functional compensation in addition to surgical diseases, with a perioperative mortality rate of 0.27% -0.40%.

Class III: Patients with severe complications and restricted physical activity but still capable of coping with day-to-day activities, with a perioperative mortality rate of 1.82% -4.30%.

Class IV: Patients with serious complications who have lost the ability to perform day-to-day activities, often have life-threatening conditions, and a perioperative mortality rate of 7.80% -23.0%.

Class V: Moribund patients either receiving surgery or not, have little chance for survival, and 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; therefore, good preparations should be fully made before anesthesia, and effective measures should be taken to prevent potential complications during anesthesia. Class IV patients are exposed to the most risks, even if good preoperative preparations are made, and have a very high perioperative mortality rate. Class V patients are moribund patients and should not undergo an elective surgery.

**16.2.3 Oncology-related definitions**

In this study, tumor staging is based on AJCC-8; surgical treatment follows the Japanese Gastric Cancer Treatment Guidelines, Physicians Edition, 4rd Edition, 2014.05, and other writing and recording principles follow the Japanese Gastric Cancer Statute 15th.

**16.2.4 Primary focus location**

The greater and lesser curvature of the stomach are divided into three equal parts, the U (upper), M (middle) and L (lower) areas, connected to the corresponding points. If the lesions are located

in two or more adjacent areas, they should be recorded in the order of the main portions of the lesions. Esophagogastric junction carcinoma is defined as a tumor whose tumor center is located within 5cm above and below the esophagogastric junction. According to Siewert classification, the tumor was divided into Siewert type I : the tumor center was located 1 ~ 5 cm above the esophagogastric boundary; Siewert type II : The center of the tumor was 1 cm to 2 cm above the esophagogastric boundary.Siewert type III : The tumor center is located 2 to 5 cm below the esophagogastric boundary.

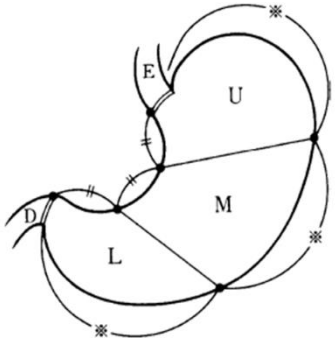



Fig. 1 The three portions of the stomach. *U* upper third, *M* middle third, *L* lower third, *E* esophagus, *D* duodenum

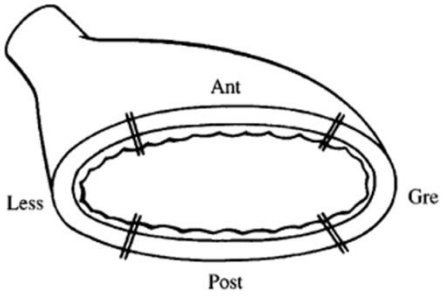



Fig. 2 The four equal parts of the gastric circumference. *Less* lesser curvature, *Gre* greater curvature, *Ant* anterior wall, *Post* posterior wall

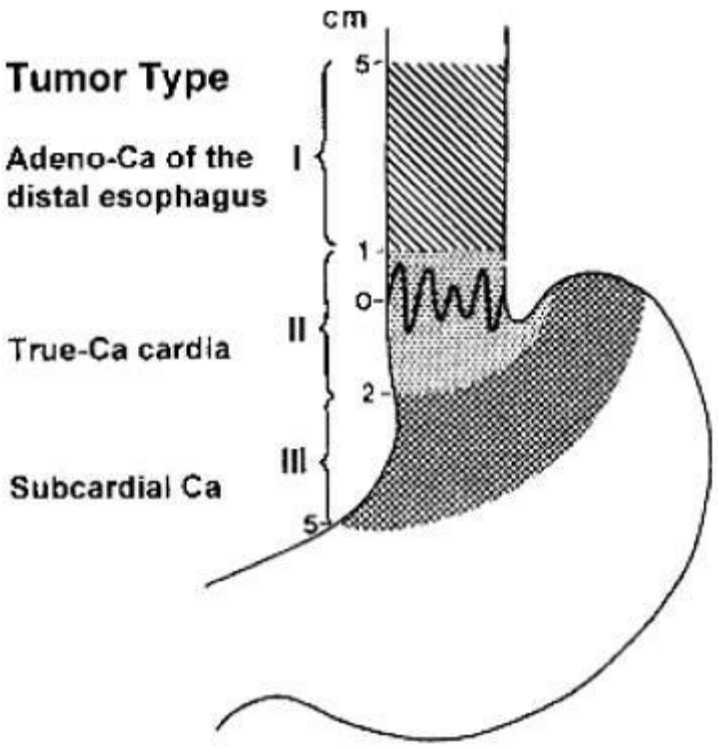



Fig. 3. Siewert type

**16.2.5 Tumor staging record**

**16.2.5.1 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<br>laparoscopy, intraoperative observations (laparotomy/laparoscopy), biopsy, cytology, biochemistry, biology examination | Pathological diagnosis of the endoscopic/surgical specimens<br>Intraperitoneal exfoliative cytology |

**16.2.5.2 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 the 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)

**16.2.5.3Records of tumor metastasis**

(1) Lymph node metastasis:

NX: Number of lymph node metastases 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

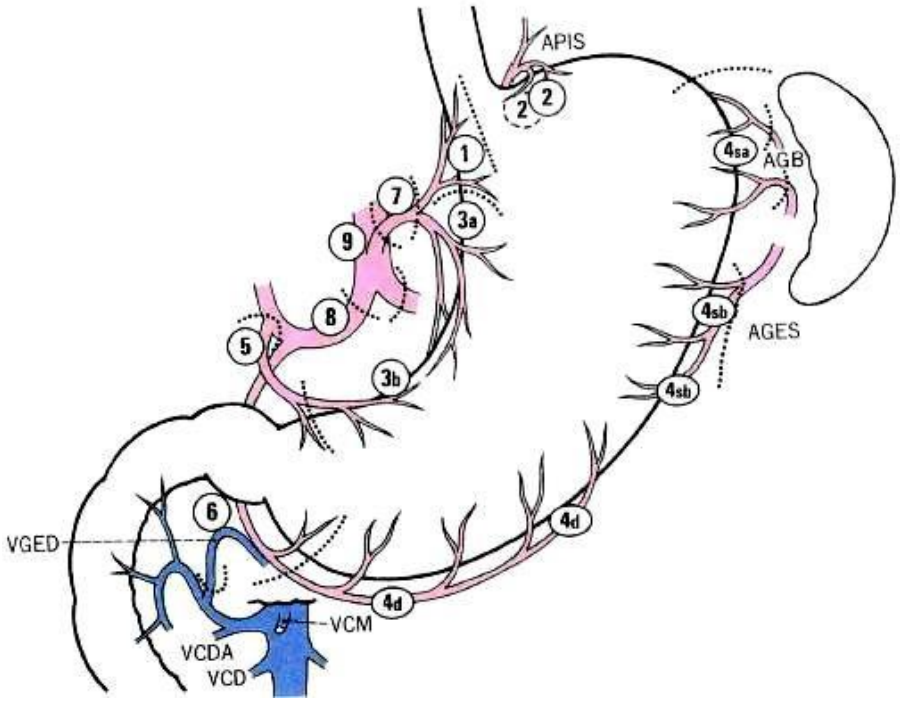
Lymph node numbers are defined as follows:

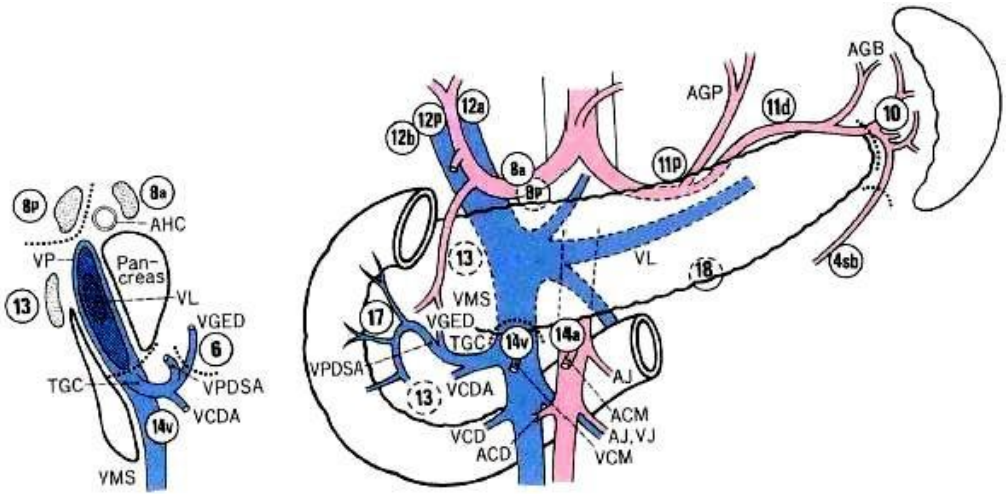
| No. | Name | Definition |
|---|---|---|
| 1 | Cardia right | Lymph nodes around the gastric wall first branch (cardia branch) of ascending branches of the left gastric artery and those at the cardia sides |
| 2 | Cardia left | Lymph nodes at the left side of the cardia and those along the cardia branch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

| | | |
|---|---|---|
| 4sb | Left side of the greater gastric curvature (along the left gastroepiploic artery) | Lymph nodes along the left gastroepiploic artery and the first branch of the greater curvature (refer to the definition of No. 10) |
| 4d | Right side of the greater gastric curvature (along the right gastroepiploic artery) | Lymph nodes at the partial left side of the first branch in the greater gastric curvature direction along the right gastroepiploic artery |
| 5 | Superior pylorus | Lymph nodes along the right gastric artery and around the first branch in the lesser gastric curvature direction |
| 6 | Inferior pylorus | Lymph nodes from the root of the right gastroepiploic artery to the first branch in the greater gastric curvature direction and those at the junction of the right gastroepiploic veins and superior anterior pancreaticoduodenal veins (including the junction portion) |
| 7 | Left gastric artery trunk | Lymph nodes from the root of the left gastric artery to the branch portion of the ascending branches |
| 8a | Anterior upper part of the common hepatic artery | Lymph nodes at the anterior upper part of the common hepatic artery (from the branch portion of the splenic artery to the branch portion of the gastroduodenal artery) |
| 8p | Posterior part of the common hepatic artery | Lymph nodes at the posterior part of the common hepatic artery (from the branch portion of the splenic artery to the branch portion of the gastroduodenal artery) |
| 9 | Surrounding of the celiac artery | Lymph gland that is in the surroundings of the celiac artery or that is a part of each root of the left artery of the stomach, common hepatic artery and splenic artery as well as that related to the celiac artery |
| 10 | Splenic hilum | Lymph gland that is in the surroundings of the celiac artery and splenic hilum far away from the end of the pancreas, including the first greater gastric curvature in the root of the short gastric artery and the left gastroepiploic artery |
| 11p | Splenic artery proximal | Lymph gland at the splenic artery proximal (in a location that divides the distance between the root of the splenic artery and the end of the pancreas into two equal parts, including the proximal side) |
| 11d | Splenic artery distal | Lymph gland at the splenic artery distal (in a location that divides the distance between the root of the splenic artery and the end of the pancreas into two equal parts, inclining to the end of the pancreas) |
| 12a | Within the hepatoduodenal | Lymph gland that is below a location that divides the height of the confluence portions of the left and right hepatic ducts and the bile |

| | | |
|---|---|---|
| | ligament (along the proper hepatic artery) | duct in the upper margin of the pancreas into two equal parts and is along the proper hepatic artery (as stated in No. 12a2 of the regulations for bile duct carcinoma) |
| 12b | Within the hepatoduodenal ligament (along the bile duct) | Lymph gland that is below a location that divides the height of the confluence portions of the left and right hepatic ducts and the bile duct in the upper margin of the pancreas into two equal parts and is along the proper hepatic artery (as stated in No. 12b2 of the regulations for bile duct carcinoma) |
| 12p | Within the hepatoduodenal ligament (along the portal vein) | Lymph gland that is below a location that divides the height of the confluence portions of the left and right hepatic ducts and the bile duct in the upper margin of the pancreas into two equal parts and is along the proper hepatic artery (as stated in No. 12p2 of the regulations for bile duct carcinoma) |
| 13 | Back of the pancreatic head | Lymph gland adjacent to the head of the duodenal papilla at the back of the pancreatic head (No. 12b in the surroundings of the hepatoduodenal ligament) |
| 14v | Along the superior mesenteric vein | Lymph gland that is in the front of the superior mesenteric vein, with the inferior margin of the pancreas on the upper side, the right gastroepiploic vein and confluence portion of the superior pancreaticoduodenal vein to the right, the left margin of the mesenteric vein to the left and the branch of the middle colic vein in the lower margin |
| 14a | Along the superior mesenteric artery | Lymph gland along the superior mesenteric artery |
| 15 | Surroundings of the colon middle artery | Lymph gland that is in the surroundings of the colon middle artery |
| 16a1 | Surroundings of the abdominal aorta a1 | Lymph gland that is in the surroundings of the aorta gap (4 to 5 cm wide in the surroundings of the medial crus of the diaphragm) |
| 16a2 | Surroundings of the abdominal aorta a2 | Lymph gland that is in the surroundings of the aorta from the upper margin of the abdominal artery root to the lower margin of the left renal vein |
| 16b1 | Surroundings of the abdominal aorta b1 | Lymph gland that is in the surroundings of the aorta from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery root |
| 16b2 | Surroundings of the abdominal aorta b2 | Lymph gland that is in the surroundings of the aorta from the upper margin of the inferior mesenteric artery root to the branch of aorta |
| 17 | Front of the | Lymph gland that is in the front of the pancreatic head, next to the |

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






血管名
略字説明

| | |
|---|---|
| APIS ····· *A. phrenica inferior sinistra* | AHC ····· *A. hepatica communis* |
| AGB ····· *Aa. gastricae breves* | VP ····· *V. portae* |
| AGES ····· *A. gastroepiploica sinistra* | VL ····· *V. lienalis* |
| VGED ····· *V. gastroepiploica dextra* | VMS ····· *V. mesenterica superior* |
| VCDA ····· *V. colica dextra accessoria* | VPDSA ····· *V. pancreaticoduodenalis superior anterior* |
| VCM ····· *V. colica media* | VCD ····· *V. colica dextra* |
| TGC ····· *Truncus gastrocolicus* | VJ ····· *V. jejunalis* |
| ACM ····· *A. colica media* | AGP ····· *A. gastrica posterior* |
| AJ ····· *A. jejunalis* | ACD ····· *A. colica dextra* |

Fig. 4. 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 the 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 for intraperitoneal exfoliated cells is recorded as M1.

**16.2.5.4Tumor Staging**

| Pathological (pTNM) | | | | | |
|---|---|---|---|---|---|
| T/M | N0 | N1 | N2 | N3a | N3b |
| T1 | IA | IB | IIA | IIB | IIIB |
| T2 | IB | IIA | IIB | IIIA | IIIB |
| T3 | IIA | IIB | IIIA | IIIB | IIIC |
| T4a | IIB | IIIA | IIIA | IIIB | IIIC |
| T4b | IIIA | IIIB | IIIB | IIIC | IIIC |
| M1 | IV | IV | IV | IV | IV |

**16.2.5.5 Pathologic types and classifications**

**16.2.5.5.1 Type**

Papillary adenocarcinoma

Tubular adenocarcinoma

Mucinous adenocarcinoma

Signet ring cell carcinoma

Poorly differentiated carcinoma

**16.2.5.5.2 Grading**

GX classification is not possible to assess

G1 well-differentiated

G2 moderately differentiated

G3 poorly differentiated

G4 undifferentiated

**16.2.5.6 Evaluation of Radical Level (Degree)**

**16.2.5.6.1 Recording the Presence or Absence 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

PM X: 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

DM X: Unknown cancer invasion on the distal incisional margin

#### 16.2.5.6.2 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