A Prospective, Multicenter, Randomized Controlled Phase III Study on the Prognostic Impact of Laparoscopic Staging in Patients with Clinical Stage III Gastric Cancer

I. Basic Study Information

II. (I) Study Title

A Prospective, Multicenter, Randomized Controlled Phase III Study on the Prognostic Impact of Laparoscopic Staging in Patients with Clinical Stage III Gastric Cancer

(II) Protocol Number

CGCA202501

(III) Study Period

Enrollment Period: December 1, 2025 – December 31, 2026
Intervention Period: From randomization to treatment completion (as determined per each center's treatment protocol)
Followup Period: From treatment completion to December 31, 2029 (minimum 3year followup)

(IV) Sponsor

Tianjin Medical University Cancer Institute & Hospital

(V) Principal Investigator

Professor Liang Han, Department of Gastric Oncology, Tianjin Medical University Cancer Institute & Hospital

Participating Institutions

See Appendix

Study Summary

Study Title	A Prospective, Multicenter, Randomized Controlled Phase III Study on the Prognostic Impact of Laparoscopic Staging in Patients with Clinical Stage III Gastric Cancer
Study Objectives	Primary Objective: To compare 3year Overall Survival (OS) between the two groups. Secondary Objectives: To evaluate the detection rate of peritoneal metastasis by laparoscopic staging in the experimental group. To evaluate the R0 resection rate after conversion surgery in both groups. To compare the surgical conversion rate (change from original treatment plan) between the two groups.
Study Design	Prospective, multicenter, randomized controlled Phase III clinical study, 1:1 randomization Experimental Group: Peritoneal metastasis (CY+ or P+), cT4aN+, or M1: Systemic therapy + NIPS ± HIPEC or HIPEC ; No peritoneal metastasis, cT3N+: Systemic neoadjuvant therapy. Control Group: Systemic therapy alone.
Inclusion Criteria	1. Pathologically confirmed: Histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II/III). 2. Definitive pathological markers: Documented status of HER2, MMR, CPS (PDL1) score, and Claudin 18.2. 3. Clinical stage: cT3/4aN+M0 based on contrastenhanced CT, endoscopic ultrasound, or MRI (AJCC 8th edition): cT3: Tumor invades through the muscularis propria into the subserosa. cT4a: Tumor penetrates the visceral peritoneum. cN+: Regional lymph node metastasis (intraabdominal regional nodes such as perigastric, celiac, or common hepatic

	artery lymph nodes: shortaxis diameter > 8 mm; other nodes such as retroperitoneal or paraaortic lymph nodes: shortaxis diameter > 10 mm). No evidence of peritoneal metastasis on imaging modalities other than laparoscopic exploration. 4. Age: 18 to 75 years, regardless of sex. 5. Performance status: ECOG score 0–2 (fully active to ambulatory and capable of selfcare but unable to work). 6. Life expectancy: Estimated survival ≥ 6 months. 7. Surgical fitness: Adequate cardiopulmonary functional reserve and no contraindications to anesthesia. 8. Informed consent: Voluntary participation with written informed consent obtained.
Exclusion Criteria	1. Gastric outlet obstruction: Requiring gastrojejunostomy due to obstructive symptoms. 2. Distant metastasis: Evidence of peritoneal, mesenteric, or omental metastasis and/or obvious ascites on imaging, or distant organ metastasis. 3. Other malignancies: History of or concurrent other malignant tumors (except curatively treated basal cell carcinoma of the skin). 4. Organ dysfunction: Severe cardiac insufficiency (NYHA class III–IV), hepatic dysfunction ChildPugh class C, or creatinine clearance < 30 mL/min. 5. Contraindications to laparoscopy: History of severe intraabdominal adhesions, coagulation disorders (INR > 1.5 or platelet count < 50×10^9/L), or severe intestinal obstruction. 6. Special populations: Pregnant or lactating women, or those

	unable to interrupt breastfeeding. 7. Mental status: Cognitive impairment or psychiatric disorders that preclude compliance with followup.
Efficacy Evaluation and Outcome Measures	Efficacy Evaluation and Outcome Measures 1. Efficacy Evaluation: Detection rate of peritoneal metastasis by laparoscopic exploration R0 resection rate after conversion surgery Surgical conversion rate (change from original treatment plan) 1year, 2year, and 3year overall survival (OS) rates 2. Followup Observation: 3year followup period 3. Assessment Methods: Laboratory examinations Imaging examinations
Sample Size	A total of 968 patients are planned for enrollment, with 484 patients in the experimental group and 484 patients in the control group, including a 20% dropout rate.
Treatment Regimen	Experimental Group: Patients undergoing laparoscopic exploration found to have peritoneal metastasis (CY+ or P+), cT4aN+, cT4bN+, or M1 disease are recommended to receive: Systemic therapy + NIPS ± HIPEC or HIPEC alone In cases without peritoneal metastasis and for patients with cT3N+:

	Systemic neoadjuvant therapy, with imaging evaluation every 3–4 cycles followed by planned surgery Nota bene: For the experimental group, systemic therapy + NIPS ± HIPEC or HIPEC is also recommended following conversion therapy surgery. NIPS Dosing (reference: PHOENIXGC study [10]): Intraperitoneal paclitaxel 20 mg/m² + IV paclitaxel 50 mg/m² (days 1, 8); q3w Or nabpaclitaxel: IP nabpaclitaxel 80 mg/m² + IV nabpaclitaxel 180 mg/m² (day 1); q3w HIPEC Dosing: Paclitaxel 40–100 mg/m² recommended If combined with NIPS: 2–4 HIPEC sessions recommended If HIPEC alone: 4 sessions recommended Control Group: No laparoscopic exploration Upfront systemic therapy without intraperitoneal drug administration Systemic Therapy (applicable to both groups): Treatment regimen selected based on molecular marker testing results and in accordance with gastric cancer treatment guidelines No limit on the number of neoadjuvant or conversion therapy cycles

	Imaging evaluation required every 3–4 cycles Surgical Treatment (applicable to both groups): Surgery performed according to each center's treatment assessment and plan Intraoperative exploration determines: 1. If R0 resection is achievable: D2 or D2+ radical gastrectomy 2. If partial response achieved but R0 resection remains infeasible: Conclude exploration, continue conversion therapy with original regimen or secondline therapy Postsurgery, maintenance therapy with the original regimen recommended until disease progression
Study Timeline	Patient enrollment is planned to be completed within 1–2 years, with a followup period of 3 years starting from the enrollment of the last patient.

II. Study Background

Study Background

According to the latest epidemiological data, gastric cancer is the fifth most common malignancy worldwide, with approximately 960,000 new cases and 720,000 deaths in 2022 [1]. In China, gastric cancer ranks fifth in incidence and third in mortality [2]. A largescale national realworld study including 220,000 patients showed that advances in early diagnosis and staging techniques and the application of novel therapies have significantly improved 5year survival rates

in gastric cancer patients, while also revealing substantial gaps in treatment standardization across hospitals in China [3]. Among surgical gastric cancer cases, clinical stage III accounts for approximately 70% (China Gastrointestinal Surgery Alliance data). These patients present with tumor invasion depth reaching the subserosa or penetrating the serosa, with regional lymph node metastasis. Conventional treatment strategies rely on clinical staging (based on CT/MRI imaging), which has a detection rate of only 20%–30% for peritoneal micrometastases (diameter <5 mm) [4]. Thinslice contrastenhanced CT is the most commonly used preoperative modality for detecting peritoneal metastasis. Although CT has high specificity for diagnosing peritoneal metastasis, its sensitivity is only approximately 50%, and 10%–30% of advanced gastric cancer patients with no evidence of peritoneal metastasis on preoperative CT are found to have occult peritoneal metastasis during intraoperative exploration [5].

Diagnostic laparoscopy + peritoneal cytology + peritoneal nodule biopsy is the most reliable method for peritoneal staging. It has high sensitivity and specificity, particularly for detecting clinically occult peritoneal metastasis, and allows relatively accurate assessment of the Peritoneal Cancer Index (PCI) and response to neoadjuvant therapy. Cohort studies including all stages of gastric cancer have shown that 14%–17% of patients have macroscopically visible peritoneal metastases, and up to 41% have positive cytology [6]. The core purpose of laparoscopic staging is to precisely identify peritoneal metastasis, thereby enabling targeted intraperitoneal therapy in addition to systemic treatment. However, there is currently no highlevel evidence regarding the prognostic impact of laparoscopic staging. The 2025 CSCO Gastric Cancer Diagnosis and Treatment Guidelines classify diagnostic laparoscopy staging as

Class IB evidence, with no support from Phase III studies. The 2025 CACA Integrated Gastric Cancer Diagnosis and Treatment Guidelines indicate that indications for laparoscopic exploration remain controversial.

The clinical challenge of peritoneal metastasis in gastric cancer lies in its high incidence and extremely poor prognosis. The peritoneum, as a metastatic site, is protected by the plasmaperitoneal barrier, which limits penetration of systemically administered drugs, leading to poor efficacy of conventional systemic chemotherapy. Current intraperitoneal treatment modalities mainly include three categories:

1. Hyperthermic Intraperitoneal Chemotherapy (HIPEC): Chemotherapy solution at approximately 42°C is perfused intraoperatively or postoperatively, leveraging thermal cytotoxicity and drug synergy to inhibit metastasis. A Chinese multicenter retrospective study showed that in gastric cancer patients with peritoneal metastasis, 3year OS was 18.4% (95% CI, 12.3%–24.5%) in the HIPEC + chemotherapy group vs. 10.1% (95% CI, 5.4%–14.8%) in the chemotherapyalone group [7].

2. Intraperitoneal Port Chemotherapy: A chemotherapy port is implanted for regular perfusion of roomtemperature drugs (e.g., paclitaxel, cisplatin). This method is convenient but carries risks of catheterrelated complications [8].

3. Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC): Drugs are aerosolized for uniform distribution within the abdominal cavity, providing excellent coverage of small lesions but requiring specialized equipment and with limited clinical application [9].

Neoadjuvant Intraperitoneal and Systemic Chemotherapy (NIPS), as an innovative approach, achieves high local drug concentrations via direct intraperitoneal administration (e.g., paclitaxel concentration in the peritoneal cavity can reach 1000 times that in plasma), combined with systemic chemotherapy to control distant metastases. The Japanese PHOENIXGC study [10] demonstrated that the NIPS group (IP + IV paclitaxel plus S1) had a median survival extension of 3.4 months compared to the control group (cisplatin plus S1) (17.7 months vs. 14.3 months, P=0.022), and 3year survival rate increased by 15.9% (21.9% vs. 6.0%). The Chinese DRAGON01 study [11] confirmed that the NIPS group achieved a median OS of 19.4 months, 5.5 months longer than the IV chemotherapyalone group, with a 21.9% increase in conversion surgery rate (57% vs. 35.1%), and patients with R0 resection achieved a median OS of 35.5 months. Compared with other methods, NIPS offers advantages including proven efficacy, high safety, broad applicability, and operational flexibility, providing a new therapeutic option for patients with peritoneal metastasis.

This study aims to determine, through a multicenter randomized controlled design, the impact of precision treatment guided by laparoscopic staging on overall survival (OS), surgical conversion rate, and peritoneal metastasis rate in patients with clinical stage III gastric cancer, thereby providing evidence for precision staging and treatment decisionmaking.

References

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III. Study Objectives

(I) Primary Objective

1. To compare 3year Overall Survival (OS) between the two groups.

(II) Secondary Objectives

1. To evaluate the detection rate of peritoneal metastasis by laparoscopic staging in the experimental group.

2. To evaluate the R0 resection rate after conversion surgery in both groups.

3. To compare the surgical conversion rate (change from original treatment plan) between the two groups.

IV. Study Design

(I) Overall Design

Study Type: Prospective, randomized controlled, multicenter Phase III clinical study

Group Allocation: Parallel assignment, Experimental group (n=[484]) vs. Control group (n=[484])

Interventions:

Experimental Group: Laparoscopic exploration reveals peritoneal metastasis (CY+ or P+), cT4aN+, cT4bN+, or M1: Systemic therapy + NIPS ± HIPEC or HIPEC. No peritoneal metastasis, cT3N+: Systemic neoadjuvant therapy. Specific drug regimens and surgical plans are determined according to guidelines (CSCO, CACA) and each center's experience.

Control Group: No laparoscopic exploration. Systemic therapy recommended based on imaging staging. Each center develops specific drug regimens and surgical plans according to current guidelines (CSCO, CACA) and their own experience.

(II) Randomization Method

1. Stratification Factor: Study center (to avoid center bias)

2. Randomization Method: 1:1 ratio between experimental and control groups using a random number table.

(III) Blinding Design

Investigator Unblinded: Surgeons are aware of group assignment (experimental group requires laparoscopic exploration).

Outcome Assessor Blinded: An independent thirdparty team assesses OS.

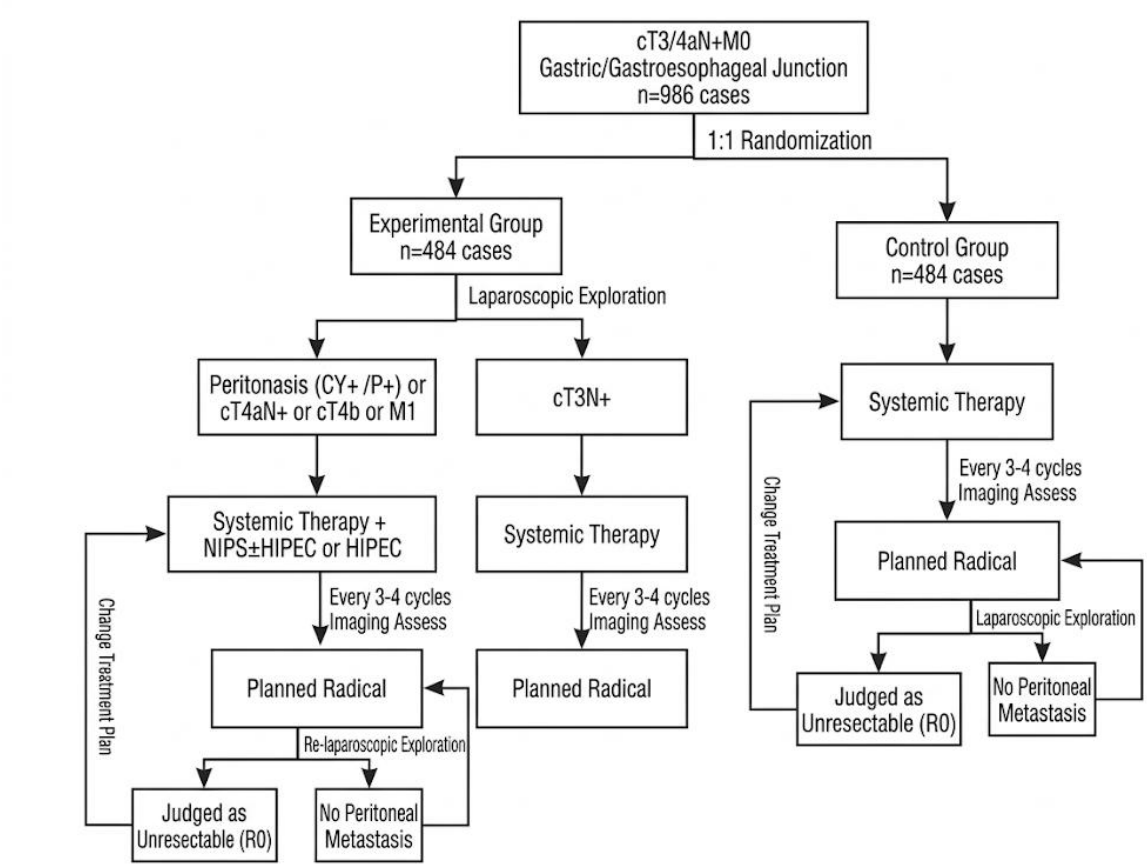
Statistical Analysis Blinded: Grouping information is concealed during statistical analysis.

(IV) Study Period

Patient Enrollment Period: All clinical research centers are expected to complete patient enrollment within one year of study initiation.

Followup Period: The enrollment of the first patient marks the start of followup. The primary endpoint followup ends 3 years after the last patient's surgery.

V. Study Flowchart



VI. Study Population

All patients who meet all inclusion criteria and none of the exclusion criteria are eligible for enrollment in this study.

(I) Inclusion Criteria

1. Pathologically confirmed: Histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert type II/III).

2. Definitive pathological markers: Documented status of HER2, MMR, CPS (PDL1) score, and Claudin 18.2.

3. Clinical stage: cT3/4aN+M0 based on contrastenhanced CT, endoscopic ultrasound, or MRI (AJCC 8th edition):

cT3: Tumor invades through the muscularis propria into the subserosa.

cT4a: Tumor penetrates the visceral peritoneum.

cN+: Regional lymph node metastasis (intraabdominal regional nodes such as perigastric, celiac, or common hepatic artery lymph nodes: shortaxis diameter > 8–10 mm; other nodes such as retroperitoneal or paraaortic lymph nodes: shortaxis diameter > 10 mm).

No evidence of peritoneal metastasis on imaging modalities other than laparoscopic exploration.

4. Age: 18 to 75 years, regardless of sex.

5. Performance status: ECOG score 0–2 (fully active to ambulatory and capable of selfcare but unable to work).

6. Life expectancy: Estimated survival ≥ 6 months.

7. Surgical fitness: Adequate cardiopulmonary functional reserve and no contraindications to anesthesia.

8. Informed consent: Voluntary participation with written informed consent obtained.

(II) Exclusion Criteria

1. Gastric outlet obstruction: Requiring gastrojejunostomy due to obstructive symptoms.

2. Distant metastasis: Evidence of peritoneal, mesenteric, or omental metastasis and/or obvious ascites on imaging, or distant organ metastasis.

3. Other malignancies: History of or concurrent other malignant tumors (except curatively treated basal cell carcinoma of the skin).

4. Organ dysfunction: Severe cardiac insufficiency (NYHA class III–IV), hepatic dysfunction ChildPugh class C, or creatinine clearance < 30 mL/min.

5. Contraindications to laparoscopy: History of severe intraabdominal adhesions, coagulation disorders (INR > 1.5 or platelet count < 50×10^9/L), or severe intestinal obstruction.

6. Special populations: Pregnant or lactating women, or those unable to interrupt breastfeeding.

7. Mental status: Cognitive impairment or psychiatric disorders that preclude compliance with followup.

(III) Discontinuation/Withdrawal Criteria

1. Poor compliance: Failure to complete ≥50% of protocolspecified followup visits or examinations.

2. Severe AE: Occurrence of studyrelated Grade 3 or higher adverse events (e.g., intestinal perforation due to laparoscopic exploration).

3. Voluntary withdrawal: Patient submits a written request to withdraw from the study.

VII. Sample Size Calculation

(I) Assumptions

Based on realworld multicenter data from China [3], the 3year OS in the control group is estimated at 48%. The experimental group is expected to achieve a 10% improvement in 3year OS. Sample size calculation uses a two independent samples survival comparison (Logrank test, approximated as comparison of two proportions). Significance level $\alpha = 0.05$ (twosided), power = 80% ($\beta = 0.2$).

Calculation Formula:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2)^2}$$

Where:

$p_1 = 0.48$ (control group)，$p_2 = 0.58$ (experimental group)，$Z\alpha/2 = 1.96$ (α=0.05, twosided)，$Z\beta = 0.84$ (β=0.2)，$p_1(1p_1) = 0.48 \times 0.52 = 0.2496$，$p_2(1p_2) = 0.58 \times 0.42 = 0.2436$，$p_1(1p_1) + p_2(1p_2) = 0.2496 + 0.2436 = 0.4932$，$(p_1\ p_2)^2 = (0.48\ 0.58)^2 = 0.01$，$(Z\alpha/2 + Z\beta)^2 = (1.96 + 0.84)^2 = 2.80^2 = 7.84$，$n = 7.84 \times 0.4932 / 0.01 = 3.866688 / 0.01 = 386.67$

Therefore, approximately 387 patients are required per group, totaling 774 patients.Considering a 20% dropout rate, the total sample size is adjusted:

$$n_{\text{total}} = \frac{774}{1 - 0.2} = \frac{774}{0.8} = 967.5$$

Rounded up, the total sample size is 968 patients, with 484 patients per group.

(II) Interim Analysis

An interim analysis will be conducted by the Independent Data Monitoring Committee (IDMC) for efficacy and safety assessment when 50% of events (approximately 484 OS events) have occurred.

VIII. Treatment Regimen

(I) Experimental Group

Patients undergoing laparoscopic exploration found to have peritoneal metastasis (CY+ or P+), cT4aN+, cT4bN+, or M1 disease are recommended to receive: Systemic therapy + NIPS ± HIPEC or HIPEC. In cases without peritoneal metastasis and for patients with cT3N+, systemic neoadjuvant therapy is recommended, with specific drug regimens and planned surgery determined according to guidelines (CSCO, CACA) and each center's experience. Notably, for the experimental group, systemic therapy + NIPS ± HIPEC or HIPEC is also recommended following conversion therapy surgery.

Laparoscopic Exploration Procedure (West China FourStep Method recommended) [12]:

1. Exploration of anterior abdominal wall and visceral surfaces: Patient in supine position. Follow a clockwise, "O"shaped route to sequentially explore bilateral diaphragmatic domes, ligamentum teres hepatis, falciform ligament, and anterior abdominal wall. Follow an "S"shaped route to sequentially explore the liver, transverse colon, left abdominal wall, left paracolic gutter, descending colon, lower abdominal wall, small intestine, right abdominal wall, right paracolic gutter, and ascending colon.

2. Exploration of pelvic cavity and visceral surfaces: Patient in Trendelenburg position. Sequentially explore the pelvic cavity and visceral surfaces, focusing on bilateral iliac fossae, bladder base, and peritoneal reflection; in female patients, also examine bilateral adnexa and uterine fundus for suspicious lesions.

3. Exploration of mesentery and small intestine: Patient returned to supine or reverse Trendelenburg position. Explore the transverse colon, small intestinal mesentery, and mesenteric root.

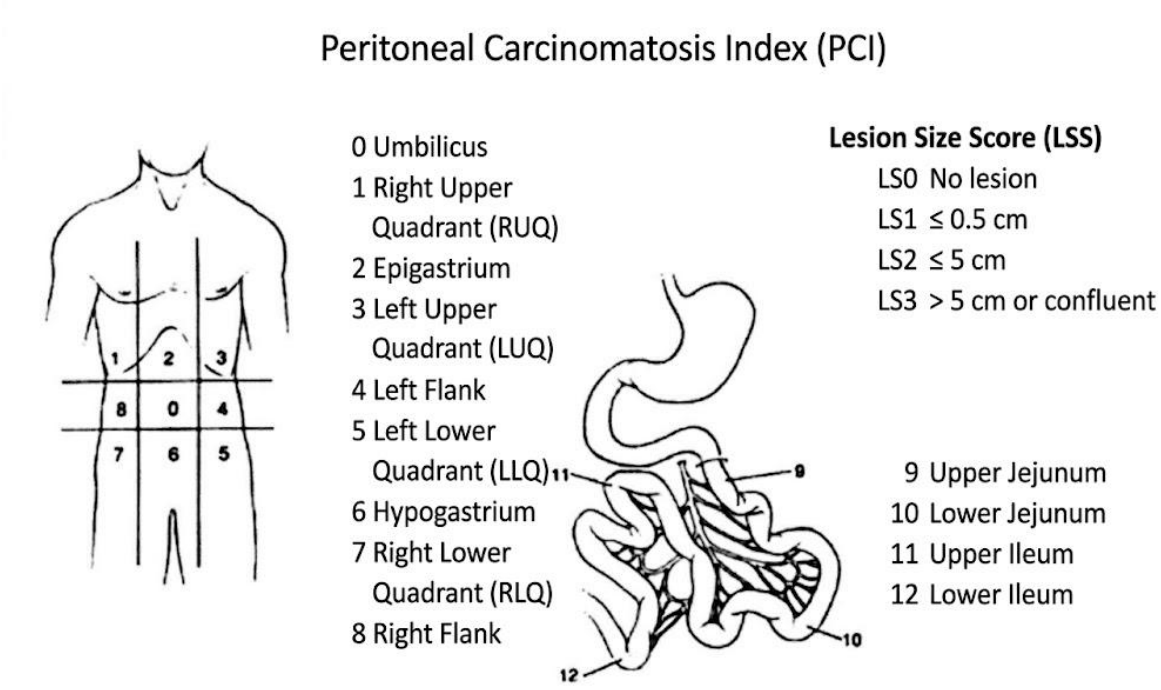
4. Exploration of stomach and perigastric region: Patient remains supine. Explore the primary gastric lesion and perigastric involvement, focusing on the lesser omentum, hepatorenal recess, and other adjacent structures for tumor invasion. A 10 mm trocar is placed at the umbilicus under general anesthesia; the laparoscope is inserted to sequentially examine the liver surface, pelvic cavity, peritoneum, perigastric area, and omentum.

Peritoneal Biopsy: For suspicious nodules (diameter ≥2 mm), biopsy from at least two sites is recommended. For highrisk biopsy sites such as the diaphragmatic dome, if peritoneal metastasis is highly suspected, photographic documentation may suffice without biopsy.

Peritoneal Free Cancer Cell Cytology Procedure:

(1) Lavage Fluid Collection: It is recommended to use >250 ml of warm saline for sequential irrigation, avoiding direct irrigation of the primary tumor and protecting the serosal surface. The irrigation sequence may proceed from bilateral diaphragmatic domes, suprahepatic, subhepatic, greater omentum, bilateral paracolic gutters, to the uterovesical and rectouterine pouches. Collect >100 ml of lavage fluid from the bilateral subphrenic spaces, subhepatic space, and pouch of Douglas for cytological examination. If sufficient ascites (>200 ml) is present, ascitic fluid may be directly collected for examination.

PCI Score: The abdominal cavity is divided into 13 regions: Central, Right Upper, Epigastrium, Left Upper, Left Flank, Left Lower, Pelvis, Right Lower, Right Flank (9 regions), and Proximal Jejunum, Distal Jejunum, Proximal Ileum, Distal Ileum (4 regions). Peritoneal lesion size score (LS) is graded as follows: LS 0: No tumor seen; LS 1: Tumor size ≤0.5 cm; LS 2: Tumor size 0.5–5 cm; LS 3: Tumor size >5 cm or confluent. Each region is assigned a score of 0–3 based on the intraoperative lesion size. A total of 13 regions are examined intraoperatively, and the LS score for each region is determined. The total PCI score (range 0–39) is the sum of LS scores for all 13 regions.



(II) Stage Determination

Clinical stage is revised based on exploration findings. If peritoneal metastasis (CY+ or P+) or micrometastases to other organs (e.g., liver metastases) are detected, the patient is classified as M1. Systemic therapy + NIPS or HIPEC or NIPS+HIPEC is recommended. For T4b, refer to the CSCO 2025 guidelines; advanced firstline conversion therapy is recommended.

(1) Intraperitoneal Therapy

HIPEC Therapy

Drainage Catheter Placement: Two drainage catheters placed in the upper abdomen (tip positioned in the left subphrenic space and hepatorenal recess) serve as inflow catheters. Two drainage catheters placed in the lower abdomen (tip positioned in bilateral pelvic floors) serve as outflow catheters. Catheters are generally placed along the anterior axillary line. Inflow catheters should ideally be positioned near tumor deposits, and outflow catheters away from tumorbearing areas.

Temperature Setting: 43°C.

Perfusion Duration: 60 minutes.

Perfusate Volume: Sufficient to achieve abdominal filling and maintain unobstructed circulation.

Perfusate: Normal saline.

Drug and Dosage: Paclitaxel, 40–100 mg/m², is recommended.

Timing: First HIPEC session to begin within 24 hours postexploration. Temperature: 43°C, Duration: 60 minutes. A minimum interval of 24 hours between HIPEC sessions is required.

Treatment Course: If combined with NIPS, 2–4 HIPEC sessions are recommended; if HIPEC alone, 4 sessions are recommended.

Intraoperative Medication: Intravenous sedatives may be administered during treatment if the patient is intolerant, with dosage adjusted according to patient response. Fluid resuscitation should be guided by vital sign monitoring.

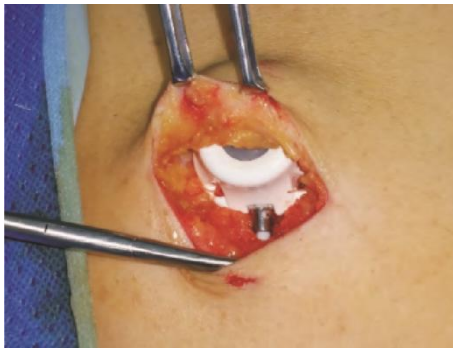
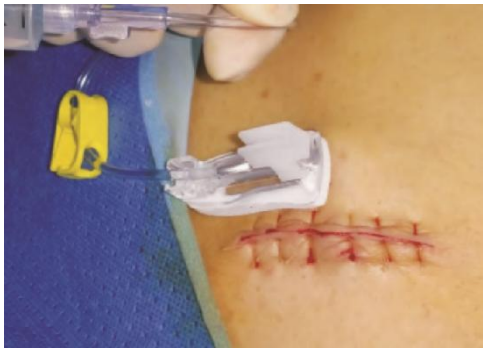
Intraoperative Monitoring: During HIPEC, monitor blood pressure, body temperature, pulse, urine output, respiration, oxygen saturation, and check for inflow catheter blockage and outflow patency. Record these parameters in the CRF at time 0, 30 minutes, 60 minutes during perfusion, and 1 hour postperfusion. If symptoms such as profuse sweating or tachycardia (>100 bpm) occur, hypovolemia should be ruled out, and fluid resuscitation intensified. If respiratory or oxygen saturation abnormalities occur, monitor anesthetic drugs and perfusate volume, and consider discontinuing treatment if necessary.

NIPS Therapy

Subcutaneous Implantation of Intraperitoneal Chemotherapy Port

The subcutaneous implantation site for the intraperitoneal chemotherapy port is typically at McBurney's point in the right lower quadrant. Depending on the patient's subcutaneous fat thickness, some adipose tissue may be excised. The base of the port is secured to the anterior rectus sheath with a single suture through a fixation hole. The intraperitoneal catheter is placed into the pelvic cavity. Strict aseptic technique should be maintained throughout the procedure

to prevent postoperative wound infection.。

NIPS Dosing: Reference PHOENIXGC study [10] dosing. Experimental group receives: Intraperitoneal paclitaxel 20 mg/m² and intravenous paclitaxel 50 mg/m² (days 1, 8); q3w. Alternatively, nabpaclitaxel: Intraperitoneal nabpaclitaxel 80 mg/m² and intravenous nabpaclitaxel 180 mg/m² (day 1); q3w.

(3) Systemic Therapy (applicable to both experimental and control groups):

Treatment regimen is selected based on molecular marker testing results and in accordance with gastric cancer treatment guidelines (including NCCN, CSCO, CACA guidelines) or participation in clinical trials. Detailed treatment regimens and doses should be recorded. There is no limit on the number of neoadjuvant or conversion therapy cycles; imaging evaluation is required every 3 to 4 cycles.

(4) Surgical Treatment (applicable to both experimental and control groups): Surgery is performed according to each center's treatment assessment and plan. Intraoperative exploration will determine the following: 1) If R0 resection is achievable, D2 or D2+ radical gastrectomy is performed; 2) If partial response is achieved but R0 resection remains infeasible, the procedure is concluded, and conversion therapy with the original regimen or secondline therapy is continued. Postsurgery, maintenance therapy with the original regimen is recommended until disease progression.

(II) Control Group

No laparoscopic exploration is performed. No intraperitoneal drug administration. Based on imaging staging, neoadjuvant therapy is recommended, avoiding immediate surgery. Each center develops specific treatment plans according to current guidelines (CSCO, CACA) and their own experience. Participation in various clinical drug trials is permitted based on actual circumstances.

Surgical Treatment: After neoadjuvant therapy, each center develops a surgical treatment plan based on assessment results. Intraoperative exploration will determine:

1) If R0 resection is achievable, D2 radical gastrectomy is performed;

2) If partial response is achieved but R0 resection remains infeasible, the procedure is concluded, and conversion therapy with the original regimen or secondline therapy is continued.

VIII. Study Endpoints

(I) Primary Endpoint

1. 3Year OS: Time from randomization to death from any cause.

(II) Secondary Endpoints

1. Peritoneal Metastasis Detection Rate in the Experimental Group:

Peritoneal metastasis detection rate = (Number of patients with peritoneal metastasis detected by laparoscopic exploration / Total number of patients in the experimental group) × 100%.

2. R0 Resection Rate After Conversion Surgery in Both Groups: Among patients with peritoneal metastasis who receive conversion therapy, the proportion of patients who undergo R0 resection.

3. Surgical Conversion Rate: In this study, surgical conversion rate refers to the proportion of patients for whom a definitive surgical treatment plan (including surgical timing, procedure type, etc.) established at enrollment is altered during the treatment course, preventing the planned surgery from being performed as intended, thereby changing the treatment strategy. Surgical Conversion Rate = (Number of patients in the control or experimental group whose original treatment plan was changed / Total number of patients in that group) × 100%. Changes to the original treatment plan include, but are not limited to: Abandoning surgery, switching to other treatments such as chemotherapy alone, adiotherapy, targeted therapy, or immunotherapy; Delaying surgery, administering other adjuvant therapies first, and reassessing operability after disease improvement; Changing the surgical approach, e.g., adjusting from planned radical surgery to palliative surgery.

IX. Followup Plan

(I) Followup Schedule

Phase	Time Point	Followup Content
Treatment Period	Before each treatment cycle	Physical examination, blood routine, liver/kidney function, tumor markers (CEA/CA199), recording of treatmentrelated adverse reactions
PostSurgery / End of	Within 1 month	Baseline CT/MRI (chest/abdomen/pelvis), wound healing assessment, etc.

Phase	Time Point	Followup Content
Treatment		
Followup Period	Years 12: Every 3 months	Clinical examination, tumor markers, chest/abdominal CT (every 6 months), inquiry about symptoms of recurrence/metastasis
	Years 35: Every 6 months	Clinical examination, tumor markers, chest/abdominal CT (annually), confirmation of survival status
PostTreatment	Annually (after 5 years)	Survival status confirmation (telephone followup)

(II) Endpoint Event Confirmation

OS Event: Confirmed through hospital medical records, death certificate, or notification by family members.

X. Data Collection and Management

(I) Data Collection Tools

1. Electronic Case Report Form (eCRF): Data entered via EDC system, including:

Baseline Data: Demographics, medical history, imaging reports, pathology results

Treatment Records: Laparoscopic procedure details (experimental group), surgical method, chemotherapy regimen, radiotherapy dose

Followup Data: Survival status, adverse events, quality of life scores, etc.

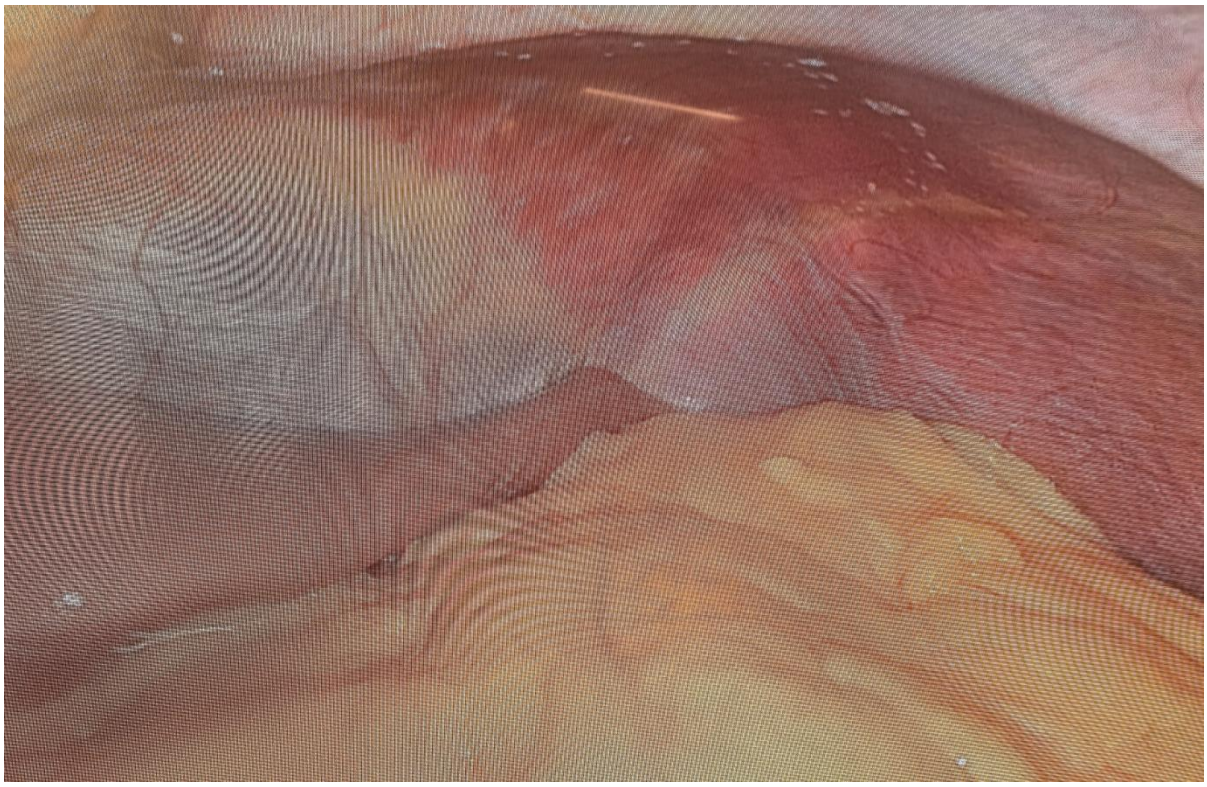
2. Imaging and Photographic Documentation

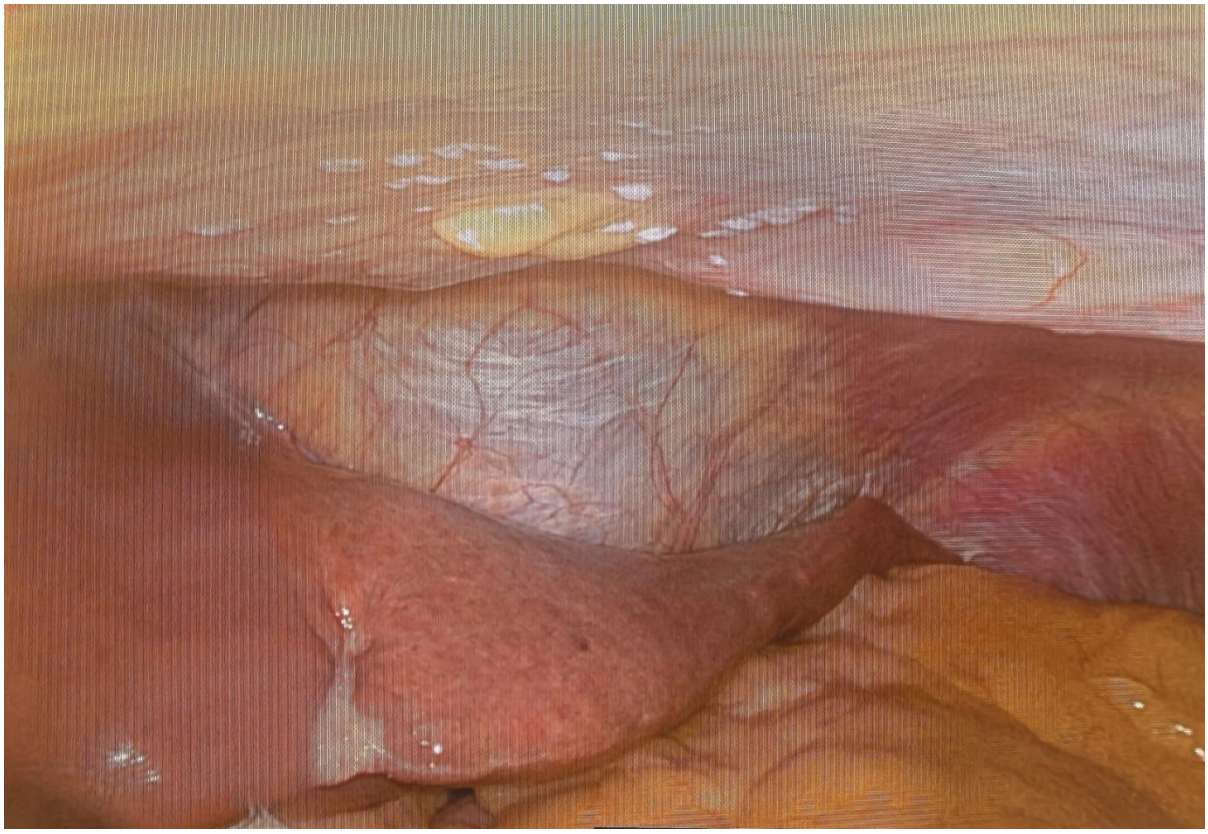
1. Retain all preoperative CT images for all enrolled patients.

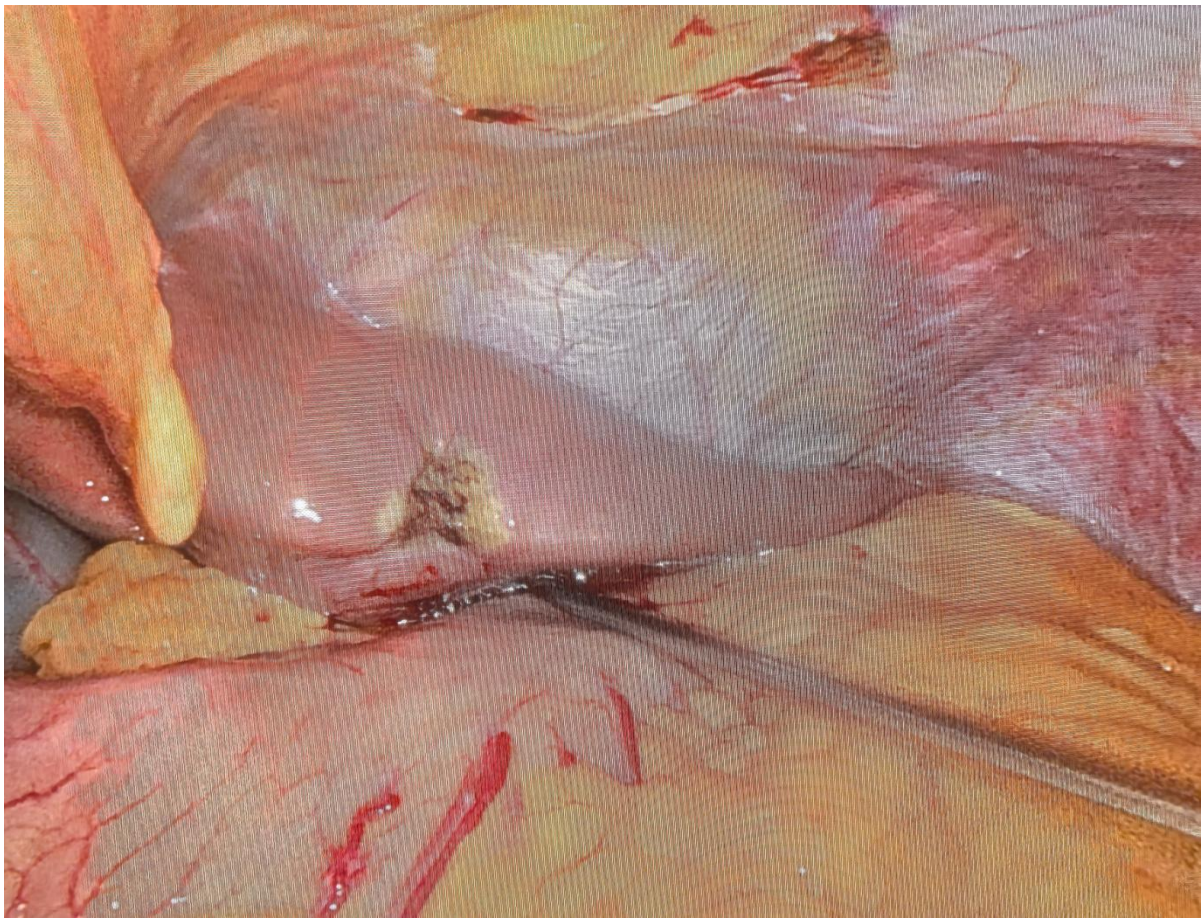
2. Preserve highquality intraoperative images of peritoneal metastasis sites and complete unedited video recordings of the entire surgical procedure.

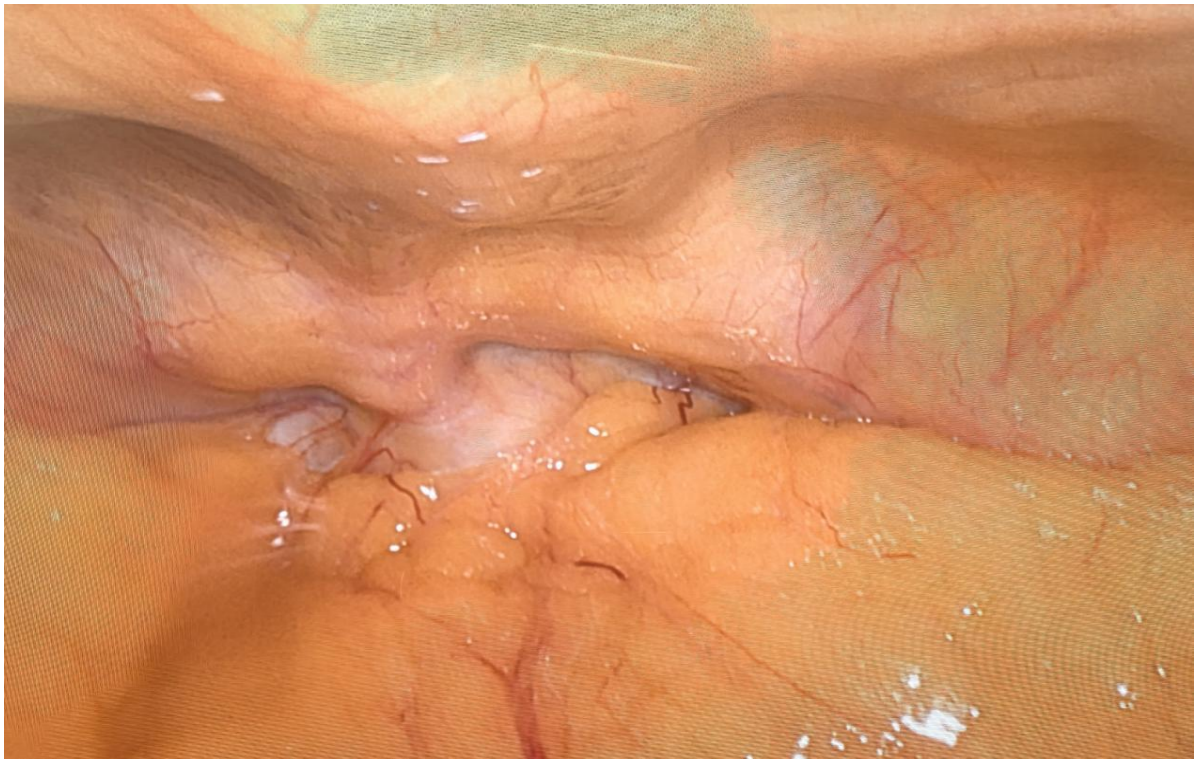
PCI scoring requires division into 13 regions. Retain images of metastatic regions, ensuring that the PCI score can be clearly calculated from the retained images and is consistent with the score recorded in the CRF.

Example: Preoperative cT4aN0M0, exploratory staging reveals peritoneal metastasis, PCI 6, liver
metastasis?









3. Postoperative Pathology Following D2 Lymph Node Dissection: Postoperative TNM staging, number of lymph nodes dissected and number of positive nodes per station, total number of nodes dissected, etc.

(II) Quality Control

Double Data Entry Verification: Key data (randomization date, endpoint event dates) will be entered independently by two designated personnel. Consistency rate must be ≥99%.

Database Lock: Following the final followup visit, the database will be locked after review and confirmation by the IDMC.

XI. Quality Assurance

(I) Investigator Training

Unified training will be conducted prior to the study initiation meeting. Training content includes: a. Each center designates 1–2 senior attending radiologists to determine TNM staging based on contrastenhanced CT or MRI. b. Standardized laparoscopic exploration procedure (refer to West China FourStep Method [12]). c. eCRF completion requirements and timelines. d. Endpoint event determination criteria (AJCC 8th edition staging update interpretation), assessed by the previously designated senior attending radiologists.

(II) Site Monitoring

Routine Monitoring: Onsite monitoring will be conducted quarterly to verify informed consent signing, CRF completeness, and specimen storage compliance.

Source Data Verification: 20% of cases will be randomly selected to verify consistency between source medical records (surgical reports, imaging reports) and eCRF data.

(III) Independent Data Monitoring Committee (IDMC)

Composition: 3 clinical oncologists, 1 biostatistician, 1 ethicist (none involved in this study).

Responsibilities: Review safety data every 6 months. Recommend suspension of enrollment if the incidence of laparoscopyrelated serious adverse events exceeds 5%.

XII. Ethical Considerations

(I) Informed Consent Process

1. Investigators will explain the following to patients in lay language:

Purpose of laparoscopic exploration (detection of micrometastases) and risks (bleeding/infection rate approximately 12%).

Fairness of randomization; both groups receive guidelinerecommended treatment.

2. Patients are permitted to withdraw from the study at any stage without affecting subsequent medical care.

(II) Risk Mitigation

Laparoscopic exploration will be performed by associate chief physicians or higher who have experience with ≥50 laparoscopic gastric cancer surgeries.

Serious adverse events (e.g., intestinal perforation) must be reported to the Ethics Committee and the sponsor within 24 hours.

(III) Ethical Review

The study protocol must be approved by the Ethics Committee of each participating center (approval number must be recorded in the CRF).

Protocol amendments (e.g., sample size adjustment) require resubmission for ethical review.

XIII. Statistical Analysis Plan

(I) Baseline Analysis

Continuous variables: Independent samples ttest (normal distribution) or Wilcoxon ranksum test (skewed distribution).

Categorical variables: Chisquare test or Fisher's exact test.

(II) Efficacy Analysis

1. Survival Analysis:

KaplanMeier method to plot OS curves; Logrank test for betweengroup differences.

Cox proportional hazards model to analyze independent prognostic factors (including laparoscopic staging, T/N stage, treatment regimen, etc.).

2. Peritoneal Metastasis Rate: Chisquare test to compare differences between the experimental group (intraoperative detection) and the control group (followup detection).

(III) Safety Analysis

Treatmentrelated adverse events will be graded according to CTCAE Version 5.0. Betweengroup comparisons will use Fisher's exact test.

(IV) Software Tools

Statistical analysis will be performed using SAS version 9.4. Survival curves will be generated using GraphPad Prism version 9.

XIV. Study Timeline

Phase	Time Period	Key Tasks
Preparation Phase	2025.06–2025.12	① Complete ethical reviews and center contracts ② Train study team ③ Set up EDC system
Enrollment Phase	2026.01–2027.12	① Monthly investigator meetings (online) ② Quarterly enrollment progress

Phase	Time Period	Key Tasks
		reports
Follow-up Phase	2026.04–2028.12	① Complete follow-up assessments per schedule ② Semi-annual study data backup
Analysis Phase	2029.01–2029.03	① Data cleaning and database lock ② Complete statistical analysis report
Reporting Phase	2029.04–2029.06	① Draft and submit study manuscript ② Hold results dissemination meeting

XV. Risk Assessment and Mitigation

(I) Major Risks and Countermeasures

Risk Type	Specific Issue	Mitigation Measures
Slow Accrual	< 2 patients enrolled per center per month	① Increase number of collaborating centers (planned expansion to 20) ② Develop patient education video (explaining advantages of laparoscopy)
Missing Data	Follow-up dropout rate > 20%	① Establish dedicated follow-up team (telephone/home visits) ② Analyze reasons for dropout
Laparoscopic Complications	Intraoperative bleeding requiring conversion to open surgery	① Preoperative coagulation assessment ② Prepare hemostatic devices (ultrasonic shears/vascular clips)
Treatment Heterogeneity	Significant inter-center variation in chemotherapy regimens	① Develop core chemotherapy drug list (e.g., XELOX/SOX regimens prioritized)

Risk Type	Specific Issue	Mitigation Measures
		② Periodic review of treatment records

XVI. Post-Trial Provisions

(I) Data Archiving

- Original data (CRFs, imaging materials) will be stored in a biorepository designated by the sponsor for 15 years.

- Anonymized data may be made available to academic institutions for secondary analysis (subject to a data sharing agreement).

(II) Patient Follow-up

- After study conclusion, patients may opt to continue in each center's routine follow-up system to provide ongoing survival status information.

(III) Results Dissemination

- Study results will be disseminated promptly through academic conferences (e.g., ASCO/HICCO) and peer-reviewed journal publication.