Research Center No. Subject's abbreviated name Patient Number

Informed Consent Form

1. Background

Gastric cancer is one of the most common malignant tumors worldwide, with persistently high incidence and mortality rates. The disease burden is particularly severe in East Asian countries such as China. The vast majority of patients are already at an advanced stage at the time of initial diagnosis, presenting with distant organ or peritoneal metastases, and are clinically defined as having stage IV gastric cancer. Traditionally, such patients have been considered to have lost the opportunity for curative treatment, and palliative chemotherapy remains the mainstay of therapy, with a median overall survival (OS) of only 10 to 13 months and an extremely poor prognosis, posing a major challenge in the field of gastrointestinal oncology[1].

In recent years, landmark advances have been achieved in the field of oncology. The application of targeted therapies, such as trastuzumab for HER2-positive cases and zolbetuximab targeting claudin18.2, along with immunotherapies, including the PD-1 inhibitors nivolumab and pembrolizumab, has significantly improved the objective response rate (ORR) and disease control rate (DCR) in advanced gastric cancer, fundamentally transforming the treatment landscape[2, 3]. Against this backdrop, the strategic concept of "conversion therapy" has emerged. Its core principle lies in delivering potent upfront systemic treatment to downstage initially unresectable advanced tumors to a state where microscopically negative resection (R0 resection) can be achieved, thereby offering patients a potential opportunity for cure. This approach represents the latest frontier in the treatment of advanced gastric cancer[4].

Multiple prospective phase II studies and retrospective analyses have provided encouraging data in this regard. For instance, the FLOT series of studies have suggested that among patients with limited metastases who achieve a favorable response to conversion therapy and undergo R0 resection, the median overall survival (OS) can exceed 30 months, with a significantly improved 5-year survival rate[5]. Similarly, the China-Japan-Korea GC-01 retrospective study also confirmed that R0 resection following successful conversion therapy is the strongest independent prognostic factor affecting long-term survival in these patients[6, 7]. Based on these data, for patients who achieve significant radiological remission (PR or CR per RECIST 1.1 criteria) following conversion therapy and are deemed by a multidisciplinary team (MDT) assessment to be amenable to R0 resection, the proactive recommendation of curative-intent surgery has become standard practice in leading medical centers worldwide.

However, the evidence supporting this aggressive surgical strategy is derived predominantly from non-randomized controlled studies, which are inherently subject to substantial selection bias and confounding factors. Patients who successfully undergo

surgery tend to be a "privileged population"—younger, with better performance status, lower metastatic burden, and more favorable tumor biology. To what extent can their superior survival outcomes be attributed to the surgical intervention itself, and to what extent do they merely reflect the intrinsically indolent biological behavior of their tumors? This is a pivotal question that cannot be definitively answered through non-randomized study designs[8]. Surgery itself is a highly invasive intervention, associated with significant perioperative mortality and morbidity risks, and may lead to interruption of subsequent effective systemic therapy. Therefore, we are confronted with a serious clinical ethical dilemma: are we "overtreating" patients who have achieved an excellent response to drug therapy? Are we subjecting a subset of patients—those whose disease could be stably controlled through highly effective medical treatment—to unnecessary surgical trauma and financial burden, without conferring additional survival benefit?

Currently, no prospective, randomized controlled phase III clinical trial designed to address this question has been reported worldwide. The absence of high-level evidence for this critical decision has led to considerable variability and inconsistency in global clinical practice. Patients' treatment choices depend more on the philosophical orientation of the multidisciplinary team (MDT) at the treating institution than on standardized criteria—a situation that is clearly suboptimal and urgently requires resolution.

Therefore, the core objective of this study is to confront the most pressing clinical equipoise at the forefront of the field: For patients with advanced metastatic gastric cancer who achieve significant radiological remission following conversion therapy, does the addition of curative-intent surgical resection to continued optimal medical therapy confer a definitive survival benefit? Answering this question is of paramount importance and urgency, as it directly impacts treatment decisions, quality of life, and survival outcomes for a large number of patients.

The innovation and scientific merit of this study lie in its being the first multicenter, randomized controlled phase II trial designed to directly compare the efficacy of "surgery + postoperative adjuvant therapy" versus "continued medical therapy alone" in this specific patient population, thereby eliminating selection bias and establishing causal relationships. We strictly define the enrollment population as patients who achieve "significant radiological remission and are deemed technically amenable to R0 resection by MDT assessment," ensuring cohort homogeneity and the targeted nature of the research question. The primary endpoint is progression-free survival (PFS), with secondary endpoints including overall survival (OS), R0 resection rate, quality of life (QoL), and treatment-related toxicities, enabling a comprehensive evaluation.

This study holds substantial scientific significance and clinical value. Its findings will provide Level 1 evidence to guide treatment strategies for this population. Should the surgery group demonstrate superiority, the role of surgery will be firmly established and promoted as a standard of care. Conversely, if the results are negative (equivalence or

inferiority of the surgery group), a large number of patients will be spared unnecessary surgical trauma, and treatment paradigms will shift back toward systemic therapy as the core approach, thereby altering global clinical guidelines. Furthermore, the study carries important health economic implications, helping to allocate limited medical resources to patients who are truly likely to benefit. Exploratory analyses of biospecimens may also deepen our understanding of the biological behavior of advanced gastric cancer, providing clues for more precise patient selection in the future.

This study is highly feasible. Conversion therapy for advanced gastric cancer is currently a research hotspot, with major centers having accumulated extensive MDT and patient management experience. The patient population with advanced gastric cancer is large, and patients generally show high willingness to participate in protocols offering potential curative opportunities. The RCT design, follow-up procedures, and statistical analysis methodologies are all well-established techniques.

In summary, conversion therapy for advanced metastatic gastric cancer represents the future direction, yet the necessity of surgery remains a critical unresolved issue. Current surgical recommendations based on non-randomized studies may harbor substantial bias. There is an urgent need for this rigorously designed randomized controlled trial to provide high-level evidence for scientifically sound clinical decision-making, avoiding both overtreatment and undertreatment, and ultimately maximizing patient survival benefits. This study has a clear objective, strong innovation, substantial significance, and full feasibility, with the potential to yield practice-changing results.

2. Objective

To compare the 2-year progression-free survival (PFS) rate between patients with advanced metastatic gastric cancer who achieve radiographic remission (CR/PR) after conversion therapy and receive surgery plus adjuvant therapy versus those who continue with drug therapy alone.

3. Research Plan

If you agree to participate in the study, you will receive the following protocol:

All enrolled subjects are patients with advanced metastatic gastric or gastroesophageal junction adenocarcinoma (with ≤2 organs involved and ≤3 metastatic lesions per organ), who have received 4 or more cycles of standard conversion therapy (chemotherapy±immunotherapy±targeted therapy). After multidisciplinary team (MDT) discussion, the primary lesion is deemed resectable (according to JGCA criteria), metastatic lesions have achieved radiological PR/CR (RECIST 1.1 criteria), and the

patient's physical condition permits surgery. All subjects who sign the informed consent form will be randomly assigned in a 1:1 ratio to either Group A (surgery group) or Group B (non-surgery group) for treatment.

All complications within 30 days post-surgery will be recorded (Clavien-Dindo classification). All subjects will be followed up every 3 months during the first 2 years after surgery, and every 6 months during the third year. Follow-up assessments include physical examination, tumor markers (CEA, CA19-9), contrast-enhanced CT of the chest, abdomen, and pelvis (every 3 months), and gastroscopy (annually). Adverse events and quality-of-life questionnaires will also be recorded concurrently.

4. **Research Procedures：**

This study is expected to enroll a total of 126 patients within 3 years. If you agree to participate in the study, the doctor will conduct a screening for you, which includes inquiring about your medical history and current condition, as well as performing relevant examinations. Your eligibility for the study will be determined according to the criteria specified in the research protocol. If you meet the study criteria, you will be enrolled in this clinical trial.

If you agree to participate in this study, each subject will be assigned a unique identification number and a medical record file will be established.

As a study subject, you have the following obligations: to provide truthful information regarding your medical history and current health status; to inform the study doctor of any discomfort you experience during the study period; not to take any anti-tumor medications during the trial; and to inform the study doctor whether you have recently participated in or are currently participating in any other studies.

4.1 Screening Period:

Initial diagnosis of advanced metastatic gastric or gastroesophageal junction adenocarcinoma (metastases involving ≤2 organs, with ≤3 lesions per organ), including:

a. Retroperitoneal enlarged lymph nodes (para-aortic, inter-aortocaval, peripancreatic, or mesenteric lymph nodes);

b. Limited peritoneal metastasis (P1a, PCI≤6);

c. Organ metastases:

- Liver metastasis: ≤5 lesions that are resectable or amenable to radiofrequency ablation;
- Lung metastasis: Unilateral involvement with resectable tumors;

-Ovarian metastasis: Unilateral or bilateral Krukenberg tumors without evident peritoneal metastasis;

- Adrenal metastasis: Unilateral or bilateral adrenal metastases;

d. Extra-abdominal lymph node metastasis (involving supraclavicular or cervical lymph nodes).

4.2 Conversion Therapy:

Receipt of standard conversion therapy regimens (chemotherapy±immunotherapy ±targeted therapy) for at least 4 cycles. (This study does not intervene in the choice of conversion therapy; regimens are selected according to guidelines, molecular subtyping, or patient condition.)

4.3 **Radiographic Assessment and Enrollment:** Following multidisciplinary team (MDT) discussion, patients whose primary tumor is deemed resectable (per JGCA criteria), who achieve radiographic PR/CR (per RECIST 1.1) for metastases, and who are physically fit for surgery are randomized in a 1:1 ratio into:

Arm A (Surgical Arm): Radical resection (primary tumor + metastases) followed by postoperative adjuvant medical therapy.

- Laparoscopic exploration is performed preoperatively to assess peritoneal metastasis status.
- The primary tumor must be radically resectable.
- R0 resection of metastases:
  - Retroperitoneal enlarged lymph nodes: Radical lymph node dissection;
  - Limited peritoneal metastasis (P1a, PCI ≤ 6): Radical resection;
  - Organ metastases:
    - Liver metastasis: Anatomical resection / radiofrequency ablation;
    - Ovarian/adrenal/lung metastases: Adnexectomy / adrenalectomy / lung resection;
  - Extra-abdominal lymph node metastasis (involving supraclavicular or cervical lymph nodes): Radiotherapy.

Arm B (Non-Surgical Arm): Continuation of the original medical therapy until disease progression or unacceptable toxicity.

4.4 Follow-up Period:

Follow-up Schedule: All complications are recorded within 30 days post-surgery (graded per Clavien–Dindo classification); during the first 2 years post-surgery, follow-up is conducted every 3 months; during years 3–5, every 6 months; and annually thereafter.

Follow-up Assessments: Include physical examination, tumor markers (CEA, CA19-9), contrast-enhanced CT of the chest, abdomen, and pelvis (every 3 months), and gastroscopy (annually). Adverse events and quality-of-life questionnaires are also recorded.

Management of Tumor Recurrence or Progression: Upon confirmed recurrence, the subsequent treatment plan is formulated by the MDT and documented until the study endpoint.

5. Matters Need Attention：

You should be aware of the following:

1) In most cases, subjects will receive treatment according to the routine provisions outlined above.
2) After surgery, subjects will undergo follow-up and re-examination every 3 months for efficacy evaluation, and survival status will be monitored. The specific re-examination items include: gastrointestinal tumor markers (every 3 months); contrast-enhanced CT of the chest, abdomen, and pelvis (every 3 months). After 2 years, follow-up and re-examination will be conducted every 6 months for efficacy evaluation, and survival status will be monitored. The specific re-examination items include: gastrointestinal tumor markers (every 6 months); contrast-enhanced CT of the chest, abdomen, and pelvis (every 6 months). However, if your doctor deems it necessary, additional examinations may be performed at any time.
3) If you participate in the study, please adhere to the treatment plan arranged by your doctor. If you experience any discomfort, please inform your doctor promptly. If the doctor decides to discontinue the study treatment, he/she will discuss the next treatment plan with you.
4) After the completion of the study, your study doctor will continue to keep in touch with you.
5) If another doctor invites you to participate in other clinical trials, please inform him/her that you are currently participating in this study.

6. Risk:

Some patients and doctors may have concerns about being randomly assigned to the non-surgical group. It is necessary to enhance communication among the multidisciplinary team, emphasize clinical uncertainties, and complete the informed consent process.

7. Benefits：

This study is built upon previous clinical research. Throughout the entire study period, you will be examined, treated, and followed up by experienced designated medical personnel. Compared with the non-surgery group, the surgery group is expected to ensure superior survival outcomes while significantly reducing overtreatment and improving quality of life.

8. Costs:

This study project follows routine guideline-based treatments, and there are no additional medication costs. All follow-up re-examination items, such as tumor markers, gastroscopy, and contrast-enhanced CT, are routine post-surgery examinations for patients and are not additional tests required specifically for this clinical study. The study group does not provide sponsorship or fee waivers.

9. Privacy:

If you decide to participate in this study, your participation and all personal data collected during the trial will be kept confidential. Information that could identify you will not be disclosed to individuals outside the research team unless your permission is

obtained. All research staff and study sponsors are required to keep your identity confidential. Any publication of study results will not disclose any of your personal information.

10. Participation/Withdrawal:

Whether or not to participate in this study is entirely your own decision. If you decline to participate, you will not be subject to any adverse effects, including the medical treatment and care you are entitled to receive. If you decide to participate, you will be given this informed consent form to sign. Even if you decide to participate, you may withdraw from the study at any time. Withdrawal from the study will not affect the standard of treatment you are entitled to receive.

In addition, if the physician implementing the study (the "study physician") determines that continued participation is no longer in your best interest, he/she may decide to withdraw you from the study.

If you decide to terminate study treatment, the doctor may still obtain follow-up information from your future medical records.

11. Compensation:

If any study-related injury occurs, the sponsor will provide compensation in accordance with applicable laws.

12. **Contact Information：**

You may obtain information and updates regarding this study at any time. If you have any questions related to this study, or if you experience any discomfort or injury during the study process, or if you have any concerns regarding the rights of participants in this study, you may contact _____ (phone number) to reach _____ (name of the investigator or relevant personnel).

Before you sign the consent form, if there is anything in this document that you do not understand, or if you have any questions, please ask your doctor. Before you decide whether to participate in this study, please read this entire document carefully and discuss it with your doctor or anyone you think is appropriate to consult (such as your family members). Only after you have signed and dated the consent form can your doctor conduct a comprehensive evaluation to determine whether you are suitable for participation in this study.

Statement

1) I understand the purpose, expected benefits, and risks of this study. I understand that the study physician has the responsibility to provide me with any additional information regarding the study itself and any injuries resulting from the study.
2) I understand that my participation in this study is voluntary, and that I may refuse to participate and/or withdraw my consent at any time and discontinue my participation in this study without any penalty or loss of any other benefits to which I am entitled.

3) Within the scope of this study, I agree that my research data may be processed in a confidential manner by the research center staff and health regulatory authorities. I agree that even if I withdraw from the trial, the data already collected about me may still be used.
4) I hereby sign this consent form to indicate that I voluntarily agree to participate in this study. I acknowledge that the study treatment is an experimental therapy and carries risks.
5) My name or any information that could identify me as a participant in this study will not be disclosed, except as required by laws and regulations or as authorized by myself/my legal representative.

I declare that I have truthfully answered the doctor's questions regarding my medical history and agree to accept the arrangements made by the study physician for me.

After signing the consent form, I will receive a copy.

Subject's Name: _____ Date: _____

Witness Signature: _____ Date: _____

Investigator Signature: _____ Date: _____

(Note: A witness signature is required only if the subject is illiterate; if the subject lacks capacity to consent, a legal representative's signature is required.)