Phase II Randomized Controlled Trial on the Necessity of Surgery in Patients with Radiological Response After Conversion Therapy for Advanced Metastatic Gastric Cancer

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.

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2. Objectives

2.1 Primary 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.

2.2 Secondary Objectives

2.2.1 To evaluate overall survival (OS).

2.2.2 To assess post-treatment quality of life using the EORTC QLQ-C30 and STO22 questionnaires.

2.2.3 To evaluate the incidence of treatment-related adverse events (TRAEs) as assessed by CTCAE v5.0.

2.2.4 To assess the R0 resection rate and postoperative complication rate (graded according to the Clavien–Dindo classification) in the surgical group.

3. PROTOCOL

3.1 STUDY DESIGN

This is a prospective, multicenter, two-arm, open-label, phase II clinical study.

3.2 STUDY FLOW

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).

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.)

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) 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.

3.3 Procedures：

All enrolled subjects are patients with advanced metastatic gastric or gastroesophageal junction adenocarcinoma (metastases involving ≤2 organs, with ≤3 lesions per organ), who have received at least 4 cycles of standard conversion therapy regimens (chemotherapy ± immunotherapy ± targeted therapy). Following multidisciplinary team (MDT) discussion, patients whose primary tumor is deemed resectable (per JGCA criteria), who achieve radiographic PR/CR for metastases (per RECIST 1.1 criteria), and who are physically fit for surgery will be randomized in a

1:1 ratio into Arm A (surgical arm) and Arm B (non-surgical arm) after signing informed consent. All complications are recorded within 30 days post-surgery (graded per Clavien–Dindo classification). For all subjects, follow-up is conducted every 3 months during the first 2 years post-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 are also recorded.

3.4 Stratification Analysis

3.4.1 Metastasis Pattern

a. Single-organ metastasis (e.g., liver-only, peritoneal-only CY1P0, etc.)

b. Multi-organ metastasis

3.4.2 Conversion Therapy Regimen

a. Containing immune checkpoint inhibitors (e.g., PD-1/L1 inhibitors)

b. Without immune checkpoint inhibitors (chemotherapy ± targeted therapy only)

3.4.3 Primary Tumor HER2 Status

a. HER2-positive (IHC 3+ or IHC 2+/FISH+)

b. HER2-negative

3.5 Sample Size Calculation

The primary endpoint of this study is the 2-year progression-free survival (PFS) rate. Based on existing literature and our institutional pilot data, we hypothesize that the 2-year PFS rate in the continued medical therapy arm (non-surgical arm) is 15%, while that in the combined surgery and adjuvant therapy arm (surgical arm) is 35% (an absolute difference of 20%). With a significance level of $\alpha = 0.05$ (one-sided) and a power of $1 - \beta = 0.8$, the sample size was calculated using the formula for superiority design comparing two independent proportions. The calculation yielded 57 patients per arm, for a total sample size of 114 patients. Accounting for an anticipated dropout rate of 10%, the final adjusted planned sample size is 126 patients, randomized in a 1:1 ratio, with 63 patients in Arm A (surgical arm) and 63 patients in Arm B (non-surgical arm).

4. Inclusion/Exclusion Criteria

4.1 Patient Postoperative Inclusion Criteria

Patients must meet all of the following criteria to be enrolled:

1. Age and Informed Consent: Aged 18 to 75 years (inclusive), voluntarily participating in this study, and having signed the patient informed consent form approved by the Ethics Committee.

2. Pathological Diagnosis: Histologically or cytologically confirmed adenocarcinoma of the stomach or gastroesophageal junction (GEJ).

3. Disease Staging: Initially diagnosed, unresectable Stage IV disease (according to the AJCC 8th edition), confirmed by the institutional multidisciplinary team (MDT) assessment as not amenable to curative surgical resection. Metastatic types include, but are not limited to: unresectable distant lymph node metastases (e.g., beyond the celiac artery trunk, supraclavicular lymph nodes, etc.); distant organ metastases (e.g., liver, lung, peritoneum, ovaries, etc.).

4. Conversion Therapy and Efficacy:

    1) Have received 4–6 cycles of first-line standard-of-care conversion therapy. The treatment regimen must be based on the latest clinical guidelines and molecular subtyping (e.g., fluoropyrimidine/platinum-based doublet or triplet chemotherapy, combined with anti-HER2 therapy [for HER2-positive patients] or immune checkpoint inhibitors [PD-1/PD-L1 inhibitors, e.g., for CPS $\geqslant$ 5 or MSI-H cases]).

    2) After completion of conversion therapy, according to RECIST 1.1 criteria, confirmed by an Independent Review Committee (IRC) or at least two senior radiologists, the efficacy has reached Complete Response (CR) or Partial Response (PR).

5. Surgical Feasibility Assessment: Re-assessed by the institutional MDT (must

include senior gastrointestinal surgeons, medical oncologists, and radiologists) and determined that all known lesions (primary tumor and metastases) are technically amenable to R0 resection, and that the patient is expected to tolerate surgery safely.

6. Performance Status: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

7. Adequate Organ Function (assessed within 14 days prior to randomization), meeting the following laboratory criteria:

   1) Hematologic system:

   Absolute neutrophil count (ANC) $\geqslant$ 1.5×10^9/L

   Platelet count (PLT) $\geqslant$ 100×10^9/L

   Hemoglobin (Hb) $\geqslant$ 90 g/L

   2) Hepatic function:

   Serum total bilirubin (TBIL) $\leqslant$ 1.5 $\times$ upper limit of normal (ULN)

   Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leqslant$ 2.5 $\times$ ULN (or $\leqslant$ 5 $\times$ ULN in the presence of liver metastases)

   3) Renal function:

   Serum creatinine (Cr) $\leqslant$ 1.5 $\times$ ULN, or creatinine clearance (Ccr) $\geqslant$ 50 mL/min (Cockcroft-Gault formula)

8. For female patients of childbearing potential, a serum pregnancy test must be negative within 7 days prior to randomization, and all patients (both male and female) must agree to use effective contraceptive methods during the study period and for 6 months after treatment completion.

4.2 Patient Exclusion Criteria

Patients meeting any of the following criteria will not be enrolled:

1. Pathological Types: Other pathological types, such as squamous cell carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, gastrointestinal stromal tumors (GIST), etc.

2. Treatment and Efficacy:

    1) Disease progression (PD) confirmed during conversion therapy.

    2) Prior systemic anti-tumor therapy for advanced gastric cancer (excluding conversion therapy).

    3) Prior radical radiotherapy to the stomach or metastatic lesions.

3. Surgery-Related Contraindications:

    1) Assessed by the MDT as having residual lesions that cannot be surgically removed (e.g., diffuse peritoneal metastases not amenable to satisfactory cytoreduction, extensive liver metastases precluding preservation of sufficient functional liver tissue, etc.).

    2) Presence of comorbid medical conditions that severely affect surgical safety and are deemed by anesthesiologists and surgeons to carry prohibitively high surgical risk, such as:

        a. Uncontrolled heart failure (NYHA Class III–IV), unstable angina, or history of myocardial infarction within 6 months.

        b. Severe chronic obstructive pulmonary disease (COPD) or other severe respiratory diseases, with expected intolerance to general anesthesia.

        c. Uncontrolled severe infections.

4. PRIOR AND COMORBID MEDICAL HISTORY:

    1) Other active malignancies within the past 5 years, with the exception of cured basal cell carcinoma of the skin, carcinoma in situ of the cervix, etc.

2) Presence of any uncontrolled serious clinical issues (e.g., severe psychiatric or neurological disorders) that would affect protocol compliance or interfere with the interpretation of study results.

5. LABORATORY ABNORMALITIES:

Presence of any severe, uncontrolled laboratory abnormalities that, in the investigator's opinion, would place the patient at significant risk by participating in this study.

6. Pregnancy and Lactation: Pregnant or breastfeeding women.

7. Others: Known severe allergy to any drugs that may be used in the study protocol (chemotherapeutic agents, targeted drugs, immunotherapeutic agents, anesthetics, etc.). Any other condition that, in the investigator's opinion, makes the patient unsuitable for participation in this clinical study.

4.3 Criteria for Withdrawal/Early Termination of the Study

Patients may voluntarily withdraw from this study at any time. The investigator may also decide to withdraw a patient from the study at any time, based on their own judgment and in consideration of the patient's specific circumstances, if it is deemed that terminating the patient's treatment would be in the patient's best interest. In the event of early study termination, the patient should return to the hospital as soon as possible to undergo the end-of-study (EOS) assessments and to begin follow-up observation. Patients should be withdrawn from the study if any of the following conditions occur:

1. Death during the clinical trial, or medical issues arising from disease progression that make it inappropriate for the patient to continue receiving the trial treatment;

2. Cases that do not meet the inclusion criteria or have irregular/incomplete documentation in the Case Report Form (CRF);

3. Patients who receive treatment regimens other than the protocol-specified regimen during the clinical trial;

4. Patients who receive any anti-cancer drug therapy, biological therapy, radiotherapy, or immunosuppressive therapy after enrollment;

5. Patients who request to withdraw from this study cohort during the clinical trial;If a patient withdraws from the trial, the reason for and time of withdrawal should be recorded in the CRF.

4.4 Exclusion Criteria

1. Failure to complete the scheduled protocol;
2. Incomplete efficacy evaluation-related data;
3. Failure to evaluate efficacy according to the scheduled protocol;
4. Management of non-compliant and discontinued cases: Non-compliant cases and those who discontinue the study should all be followed up, and should be handled according to the intention-to-treat (ITT) principle in the statistical analysis.

5. Clinical trial evaluation endpoint indicators

1. Progression-Free Survival (PFS): The time period from the initiation of conversion therapy to disease progression (e.g., tumor enlargement or metastasis) or death from any cause.

2. Overall Survival (OS): The time from the date of surgery to death from any cause (for patients lost to follow-up, the date of the last follow-up visit is used; for patients still alive at the end of the study, the date of the last follow-up visit is used).

6. Follow-up

After the subject signs the informed consent, follow-up visits will be conducted every 3 months for the first 2 years post-surgery, and every 6 months in 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. Management of recurrence: Once recurrence is confirmed, the subsequent treatment plan will be formulated by the MDT and documented until the study

endpoint.

7. FOLLOW-UP ENDPOINT

1. The patient died or withdrew from the study for some reason.
2. Obtain complete 3-year survival data.

8. Statistical Analysis

Both intention-to-treat (ITT) principle and per-protocol set (PPS) analysis will be adopted.

Primary endpoint analysis: Survival curves will be plotted using the Kaplan-Meier method, and the 2-year PFS rate along with its 95% confidence interval (CI) will be calculated.

Secondary endpoint analysis: OS will also be analyzed using the Kaplan-Meier method. Quality-of-life scores will be compared using a mixed-effects model for repeated measures. Toxicity incidence rates will be presented using descriptive statistics.

9. Ethical Consideration

This study will strictly adhere to the principles of the Declaration of Helsinki and will be submitted to the institutional Ethics Committee for review and approval prior to implementation. All patients must be fully informed and sign the consent form before participation. This study compares the effects of different treatment measures on disease prognosis; all treatment measures are conducted in accordance with current clinical medical standards, with no new methods or new drug interventions involved. Participation in the study will not cause harm to patients. Patients have the right to withdraw from the study unconditionally at any time, and this will not affect their subsequent standard treatment. The patient's health status will be closely monitored throughout the study, and once signs of recurrence appear, standard treatment procedures will be initiated immediately.