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Electro-acupuncture combined with adjuvant chemotherapy in gastric cancer (EAGER-2): a protocol for a multicenter randomized controlled trial

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Study protocol

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Abstract

Background

After undergoing gastrectomy, patients with gastric cancer frequently experience recurrence and metastasis. In our earlier research (EAGER trial, NCT04360577), we found that electro-acupuncture showed potential in extending disease-free survival (DFS) for gastric cancer patients receiving adjuvant chemotherapy. Nevertheless, the DFS data, a secondary outcome, was not yet mature, highlighting the need for robust, evidence-based studies to validate the advantages of electro-acupuncture in relation to DFS.

Methods

A multicenter, participant-blinded, sham-controlled, randomized trial involving 346 patients will be conducted in China. Participants will be allocated randomly in a 1:1 ratio to receive either electro-acupuncture or a sham acupuncture treatment (administered weekly, three times per chemotherapy cycle for four cycles) during their adjuvant chemotherapy. The selected acupoints will include GV20, EX-HN3, CV12, and bilateral PC6, ST36, SP6, SP4, and BL20. The primary outcome will be disease-free survival (DFS), while secondary measures will encompass health-related quality of life (HRQOL), symptom burden, Traditional Chinese Medicine symptom burden, overall survival, and chemotherapy completion rate.

Discussion

This study

Trial registration

The study was approved by the Ethics Committee of Guangdong Province Hospital of Chinese Medicine (approval number BF2024–351) with registration at ClinicalTrials.gov (TRN NCT07098949, Registration date 25 July 2025).

Introduction

Gastric cancer (GC) ranks as the fifth most common malignancy globally, with about 969,000 new cases in 2022, and is the fifth leading cause of cancer-related mortality, accounting for about 660,000 deaths in 2022[1]. Based on the CLASSIC trial[2, 3] and the RESOLVE trial[4, 5], gastrectomy plus D2 lymphadenectomy, followed by 8 cycles of XELOX/SOX chemotherapy are still the standard treatments for pathological stage II–III GC cases in Asia[6, 7]. In trials concerning stage II–III GC, the adjuvant chemotherapy groups reported a 3-year disease-free survival (DFS) rate ranging from 51% to 74%, while the 5-year overall survival (OS) rates varied between 52.1% and 78%[2-5, 8, 9], indicating the limited clinical advantages for patients, which restricts the effectiveness of gastric cancer therapies. Current evidence suggests that even with the addition of immune checkpoint inhibitors (ICIs) to adjuvant therapies of GC, DFS has not been prolonged[10], except those who have ever received neoadjuvant ICIs[11, 12]. Consequently, there is a growing interest among clinicians and researchers in discovering new therapeutic strategies to improve the efficacy of adjuvant chemotherapy and prolong DFS and OS.

Electro-acupuncture (EA) has demonstrated its effectiveness as a treatment approach for gastric cancer, such as reducing the duration of postoperative ileus after laparoscopic gastrectomy[13], regulating the serum tumor marker levels of patients with advanced gastric cancer and with a high safety profile[14], and prolonging progress free survival and OS of advanced gastric cancer patients completing second-line chemotherapy by reversing Th1/Th2 shift and attenuating inflammatory responses[15]. Our earlier research (EAGER trial, NCT04360577)[16-18] has also proved that EA leads to a significant enhancement in health related quality of life (HRQOL) for gastric cancer patients receiving adjuvant chemotherapy, which was the primary outcome of the study. Notably, EA was associated with a promising effect in prolonging DFS, with the 3-year DFS rate rising from 54.9% to 76.5%[16, 18]. However, the DFS findings are still in the early stages, classified as a secondary outcome, and the imaging for monitoring was determined by the physician's judgment instead of a predetermined follow-up plan. Additionally, the EAGER trial did not include a sham acupuncture group as a control, making it difficult to ascertain if the observed benefits were due to a placebo effect. Consequently, further well-designed trials with sufficient power, focusing on DFS as a primary outcome and incorporating a sham-controlled framework, are essential to validate the effectiveness of EA in prolonging DFS for gastric cancer patients.

A participant-blinded, sham-controlled, randomized trial, known as EAGER-2, will be carried out across 16 or more centers, involving 346 participants diagnosed with gastric cancer at pathological stages II or III. In contrast to its predecessor, EAGER[17], this study has been meticulously designed and enhanced based on input from a team of multidisciplinary experts, focusing on the study's objectives, protocol, and treatment strategies. EAGER-2 aims to validate the clinical efficacy of EA combined with adjuvant chemotherapy in prolonging DFS for gastric cancer patients (Aim 1) and to provide higher-level evidence for EA's efficacy in improving HRQOL during adjuvant chemotherapy (Aim 2).

Methods

The EAGER-2 trial, EA combined with adjuvant chemotherapy for prolonging DFS after radical gastrectomy, follows the Helsinki Declaration and has been approved by the Ethics Committee of Guangdong Province Hospital of Chinese Medicine (approval number: BF2024-351) with registration at ClinicalTrials.gov (TRN: NCT07098949, Registration date: 25 July 2025) prior to the first participant enrollment. In reporting the study protocol, we complied with the SPIRIT 2025 guidelines (Standard Protocol Items: Recommendations for Interventional Trials)[19].

1. Study design

A multicenter, randomized, participant-blinded, sham-controlled, parallel clinical trial will take place across 16 or more hospitals in China, including Guangdong Province Hospital of Chinese Medicine, The First Affiliated Hospital of Sun Yat-sen University, The Sixth Affiliated Hospital of Sun Yat-sen University, Foshan First People's Hospital, The Fifth Affiliated Hospital of Sun Yat-sen University, Guangdong Provincial People's Hospital, The First Affiliated Hospital of Guangzhou University of Chinese Medicine, The First People's Hospital of Zhaoqing, Foshan Hospital of Chinese Medicine, Ningxia Hospital of Integrated Traditional Chinese and Western Medicine, Peking Union Medical College Hospital, Jiangsu Province Hospital of Chinese Medicine, Hunan Cancer Hospital, Zhejiang Cancer Hospital, Guangzhou Twelfth People's Hospital, Southwest Hospital. The trial is currently expanding its sub-centers based on progress. Participants will be recruited from both inpatient and outpatient oncology and gastrointestinal surgery departments. Eligible and consented patients will be randomly allocated in a 1:1 ratio to receive either electro-acupuncture (administered weekly, three times per chemotherapy cycle) or sham acupuncture (SA, also weekly, three times per cycle) during the initial four cycles of adjuvant chemotherapy. Recurrence or metastasis will be monitored using CT/MRI imaging. Patients are advised to have CT/MRI scans every three months for the first three years post-radical gastrectomy, then every six months during the fourth and fifth years, and annually thereafter to track tumor development. HRQOL and symptom burden will be assessed at baseline (Day1 of randomization), Day 8 of each Cycle 1-4, and the last day of Cycle 4 (21 days for one cycle). The trial's design is illustrated in Fig. 1, and the measurement schedule is detailed in Table 1.

2. Participants

The inclusion criteria and exclusion criteria for the EAGER-2 trial closely mirror those established for the EAGER trial, with the following specifics outlined. Candidates meeting the following criteria will be eligible: (1) pathologically diagnosed with gastric or esophagogastric junction cancer after R0 resection and D2 lymph node dissection; (2) pathological stage II or stage III; (3) without tumor recurrence confirmed by imaging examination; (4) without chemotherapy after resection, planning to accept at least 4 cycles of adjuvant chemotherapy; (5) ECOG score ≤2 (scores range from 0 to 5, with higher scores indicating greater disability); (6) age: 18 ~75 years old; (7) normal organ function, including (7.1) bone marrow function: absolute neutrophil count (ANC) ≥1.5×10e9/L, platelet (PLT) ≥100×10e9/ L, hemoglobin (Hb) ≥90g/L; (7.2) kidney function: Serum creatinine (Scr) ≤1.5mg/dl (133μmol/L) and/or Creatinine clearance rate (Ccr) ≥60ml/min; (7.3) liver function: total bilirubin (TB) ≤1.5×upper limit of normal value (ULN), alanine transaminase (ALT) ≤2.5×ULN, aspartate transaminase (AST) ≤2.5×ULN; (8) with the written informed consent.

Patients will be excluded if they meet any of the following criteria: (1) cannot complete baseline assessment; (2) needle phobia; (3) planning to accept postoperative adjuvant radiotherapy; (4) history of hematological diseases or organ transplantation, or long term use of immunosuppressors; (5) implanted with heart pacemaker; (6) acupuncture treatment within the previous 6 weeks; (7) with active infection; (8) currently receiving or having used the investigational drug or device within 4 weeks prior to the first intervention of the study; (9) presence of other primary tumors; (10) pregnant or lactating women, psychiatric disorder, intellectual disabilities, language disabilities, lacking legal capacity, medical or ethical reasons affecting study continuation.

3. Randomization

Participants will be allocated randomly to either the acupuncture group or the sham acupuncture group in a 1:1 ratio, stratified by neoadjuvant chemotherapy (yes or no), allowing for full allocation concealment, using the central randomization system V1.0 (https://ffx.gdhtcm.com/randomization/portal/portalLogin) provided by Key Laboratory of Clinical Research Methodology in Traditional Chinese Medicine, Guangdong Province Hospital of Chinese Medicine. Allocation will be implemented using variable block lengths to prevent the investigators who will enroll or assign participants to the interventions from guessing the group assignment of the next subject and selecting subjects accordingly, thereby avoiding selection bias. The research staff at sub-centers will ensure that the informed consent forms have been obtained from each participant prior to randomization.

4. Blinding and Treatment Credibility

Treatment allocation will be concealed from the participants, outcome assessors and statistical analysts, although investigators who screened and enrolled participants will not be masked. When the treating physician and researchers plan to withdraw the patient from the study due to grade 3-4 TRAEs, unblinding is permissible and the participant will be informed of the allocated group. Credibility Rating will be adopted to evaluate the effectiveness of blinding, assessed by the Borkovec and Nau scale[20], which has been employed in various studies to evaluate the credibility and expectations surrounding acupuncture placebo controls[21-23]. Two questions will be asked at baseline (how confident are you that this treatment can alleviate your complaint? how logical does this treatment seem to you?) and two questions after all EA/SA treatment sessions (how confident

would you be in recommending this treatment to a friend who suffered the same complaint? how successful do you think this treatment would be in alleviating other complaints?). Each question will be measured on a 0-6 Likert scale with 6 being the most credible.

5. Interventions

5.1 Chemotherapy

All participants will receive adjuvant chemotherapy. Eight cycles of XELOX (oxaliplatin and capecitabine) or SOX (oxaliplatin and S-1) regimens during perioperative period will be recommended, but not mandated, according to the clinical guidelines of Chinese Society of Clinical Oncology[7]. The XELOX regimen consists of 130mg/m^2 of oxaliplatin intravenously on the first day and 1000mg/m^2 of capecitabine taken twice daily for 14 consecutive days, repeated every 21 days. The SOX regimen consists of 130mg/m^2 of oxaliplatin intravenously on the first day and 40mg/m^2 of S-1 taken twice daily for 14 consecutive days, repeated every 21 days. If the patient received neoadjuvant ICIs and is planned to undergo adjuvant XELOX or SOX regimen, the addition of adjuvant ICIs is at the discretion of the investigator, which means that adjuvant XELOX or SOX chemotherapy combined with perioperative ICIs is permitted.

5.2 Relevant concomitant treatment

Treatments for antiemesis, liver protection, myelosuppression correcting, and other chemotherapy toxicity controlling can be applied depending on treating physician's decision. While it is advisable, though not obligatory, to refrain from utilizing additional Traditional Chinese Medicine (TCM) therapies, such as herbal remedies, moxibustion, or auricular pressure during the initial four cycles of adjuvant chemotherapy. Any TCM treatments related to chemotherapy side effects or other diseases will be recorded in the case report forms (CRF).

5.3 Acupoints prescription

The selection of acupoints has been developed in accordance with findings from the EAGER trial[17], which indicated that EA may effectively prolong DFS in patients with gastric cancer receiving adjuvant chemotherapy[16-18]. The acupoints included in the prescription are Baihui (GV20), Yintang (EX-HN3), Zhongwan (CV12), Bilateral Neiguan (PC6), Bilateral Zusanli (ST36), Bilateral Sanyinjiao (SP6), Bilateral Gongsun (SP4), Bilateral Pishu (BL20).

5.4 Procedure of electro-acupuncture treatment

Typically, patients are positioned sitting for BL20, where needles are removed following the sensation of *"De qi"*, and lying down for GV20, EX-HN3, CV12, PC6, ST36, SP6, and SP4, where needles retained for 30 minutes after achieving *"De qi"*. Sterile, disposable, stainless steel acupuncture needles (25 or 40 mm length and 0.25 mm gauge; Hanyi Medical Instrument Co., Ltd Beijing) will be gently inserted into designated acupuncture points. For BL20, short needles will be inserted obliquely 15-25 mm deep at an angle of 30 degrees to skin, vertically toward the spine or away from the spine. Lifting and thrusting the needles to obtain the sensation known as *"De qi"*, a sense of soreness, warmth, tingling, or heaviness reported by patients suggested effective needling. Needles in BL20 will be removed after *"De qi"*. For GV20 and EX-HN3, needles will be inserted obliquely 10-15mm deep at an angle of 30 degrees to skin. For PC6 and SP4, needles will be inserted vertically 15-25mm deep from the skin surface. For CV12, ST36 and SP6, needles will be inserted vertically 25-35mm deep from the skin surface. An electric stimulator (SDZ-V EA apparatuses; Huatuo Industrial Co., Ltd, Suzhou, China) will be attached to the needle handles of ST36 and SP6 on the same side, avoiding crossing the spine, using a continuous wave of 2 Hz, with the current intensity adjusted to a level that the patient can feel and tolerate. After *"De qi"* is achieved, the manual needles at GV20, EX-HN3, CV12, PC6 and SP4 shall be retained for 30 minutes, along with the electro-acupuncture at ST36 and SP6 for the same period. Patients will undergo acupuncture sessions weekly, with a total of 21 days for one cycle, starting on days 1, 8, and 15 during the initial four cycles of adjuvant chemotherapy.

5.5 Procedure of sham acupuncture

The group receiving sham acupuncture will also undergo weekly sessions over a 21-day period for one cycle, with interventions occurring on days 1, 8, and 15 during the initial four cycles of adjuvant chemotherapy. This approach differs from genuine acupuncture in several key aspects: 1) instead of authentic acupuncture needles, participants will be given blunt-tipped placebo needles attached to plastic devices, which will create a slight pressure sensation and a visual cue of needle insertion but without actual skin penetration; 2) rather than puncturing the classic acupuncture points, an equal number of non-acupuncture and non-meridian points located near the study acupoints will be chosen; 3) the electric stimulator will be activated on a channel that does not deliver electrical output, allowing participants to see the lights blinking without experiencing any electrical stimulation.

The purpose of sham acupuncture is to ensure that participants receive the identical personal attention, the same intervention duration, and the credibility of the procedure without actual efficacy of acupuncture treatment. All individuals in both the real and sham acupuncture groups will be informed that they will receive a mild-stimulating acupuncture treatment. To maintain privacy and prevent interaction, patients treated in the same room will be separated by curtains.

6. Outcome measures

6.1 Primary outcome

Disease free survival

DFS is defined as the time from surgery to the occurrence of tumor recurrence, distant metastasis, or death from any cause, whichever happens first, with a follow-up period of up to five years. An independent review committee (IRC), blinded to participants' groups and consisting of at least three radiologists with a minimum of five years of clinical expertise, will be responsible for DFS. Tumor assessments (chest X-ray/CT/MRI and abdominal CT/MRI/B ultrasound) will be recommended at baseline, after the fourth chemo-cycle, henceforth once every 3 months for the initial 3 years, once every 6 months for years 4-5, and then annually until the conclusion of the study. Imaging data will be documented biannually. Should any signs of relapse arise (such as relevant clinical symptoms), additional tumor evaluations will be conducted during the treatment phase, and any potential re-surgery or further cancer interventions will also be recorded.

6.2 Secondary outcomes

6.2.1 Health-related quality of life (HRQOL)

HRQOL will be assessed by the Chinese version of Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) at baseline, Day 8 of each Cycle 1-4, and the last day of Cycle 4. HRQOL consists mainly of 6 indicators. (1) Average trajectory of FACT-Ga Trial Outcome Index (TOI) over time; (2) total area under curve (AUC) of FACT-Ga TOI; (3) average trajectory of Gastric cancer subscale (GaCS) of FACT-Ga; (4) total AUC of GaCS of FACT-Ga; (5) average trajectory of FACT-Ga scores over time; (6) total AUC of FACT-Ga scores.

FACT-Ga (Appendices) Scoring is designed for measurement of HRQOL for gastric cancer patients[24]. A validated Chinese version exists for the local population[25]. FACT-Ga comprises five distinct subscales: physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB), and GaCS. FACT-Ga includes 27 general HRQOL questions, along with 19 items specifically addressing gastric cancer symptoms, where patients rate the severity of their symptoms on a scale from 0 to 4. The overall scores vary from 0 to 184, while the GaCS focuses on gastric cancer-related symptoms and functions, with a scoring range of 0 to 76. TOI is derived from the PWB, FWB, and GaCS of the FACT-Ga, with scores ranging from 0 to 132. Higher scores reflect a better quality of life.

6.2.2 Symptom burden

Symptom burden will be assessed by modified Edmonton Symptom Assessment Scale (mESAS) at baseline, Day 8 of each Cycle 1-4, and the last day of Cycle 4. Symptom burden consists mainly of 2 indicators: (1) average trajectory of mESAS; (2) total AUC of mESAS. mESAS (Appendices) is a commonly utilized questionnaire for assessing symptoms in individuals with cancer[26-28]. It includes 11 items, each rated from 0 to 10, covering aspects such as pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, overall well-being, breathlessness, insomnia[29] and constipation[30]. The higher the score, the worse the symptom.

6.2.3 Traditional Chinese medicine symptom burden

TCM symptom burden will be assessed by MD Anderson Symptom Inventory for Traditional Chinese Medicine (MDASI-TCM) at baseline, Day 8 of each Cycle 1-4, and the last day of Cycle 4. TCM symptom burden will be measured through 2 indicators: (1) average trajectory of MDASI-TCM; (2) total AUC of MDASI-TCM. MDASI-TCM (Appendices) is a tool for patient-reported outcomes specifically aimed at gauging the intensity of various symptoms associated with TCM and their impact on the daily lives of cancer patients[31]. It is a specialized module of MDASI, which includes 13 core symptom items and 6 interference items, in addition to evaluating 7 symptoms unique to TCM with each item scored from 0 to 10. A higher score reflects a greater severity of symptoms.

6.2.4 Overall survival

OS is defined as the time from surgery until death from any reason, evaluated over a period of up to five years. Data on survival will be collected biannually.

6.2.5 Chemotherapy completion rate

Completion rate of the total planned chemotherapy duration will be calculated by patients who completed eight cycles of chemotherapy/study patient total number×100%. The start dates and actual administered dosages of every patient’s chemotherapy cycle will be recorded. A chemotherapy cycle is defined as completed or non-completed according to the treating physician’s note in consideration of actual duration and dose of both oxaliplatin and S-1/capecitabine that patients receive during a chemotherapy cycle.

6.3 Treatment-related adverse events

The incidence of treatment-related adverse events (TRAEs), graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, V5.0), will be assessed one day before each chemotherapy cycle, continuing until the EA or SA concludes. TRAEs, particularly those associated with chemotherapy like nausea, vomiting, diarrhea, constipation, oral mucositis, hand-foot syndrome, and peripheral neuropathy, will be evaluated and recorded in the CRF by research personnel who are aware of the treatment assignments. Adverse events related to acupuncture, such as fainting, needle breakage, bleeding, localized hematoma, and severe localized pain, will also be classified as TRAEs. When grade 3-4 TRAEs occurs, the treating physician and researchers will consider options such as reducing the chemotherapy dose, altering the chemotherapy regimen, or withdrawing the patient from the study, all with the goal of ensuring the subject's safety.

7. Criteria for discontinuation

Participants are entitled to exit the study at their discretion and for any reason, with the primary motivations for their departure documented. An annual review of the study will be carried out by the ethics committee. Any serious adverse events (SAEs) experienced by participants should be reported to the ethics committee of the relevant sub-centers. The ethics committee reserves the authority to discontinue the study if there are any concerns regarding patient welfare, based on the findings from the annual review and the reported SAEs.

8. Quality control

EA or SA interventions will be performed by licensed acupuncturists with at least 2 years of experience. Before treating patients, all acupuncturists will receive training on the specific intervention procedure protocol and complete study checklists. Each treatment session will be documented through photographs. The lead acupuncturists will check documentation and treatment deviations and discuss with study acupuncturists throughout the study period to ensure treatment fidelity. Acupuncture recording cards, detailed the intervention dates and specific acupoints, have to be signed by the patient and acupuncturist after each treatment. All imaging data collected during the study will be submitted to the IRC, which will perform independent assessments of tumor imaging. Before conducting evaluations, committee members will undergo training specific to the protocol and must pass a qualifying exam, with training completion also certified by the principal investigator. The results of the imaging assessments will be recorded on a standardized form, which includes the date of evaluation and the signature of the assessor to verify authenticity.

9. Data management

Patient diaries should be completed by the patient independently. All the data collected will be documented in CRF, and then entered into an Electronic Data Capture (EDC) system by clinical research coordinators. Clinical research associates will check the data to guarantee the accuracy, integrity, and traceability. An independent data monitoring committee, free from any conflicts of interest with the researchers or sponsors, will conduct random checks on the CRF data and be responsible for the data quality. All study-related documents will be archived by the investigators and preserved in Guangdong Province Hospital of Chinese Medicine for a minimum of ten years. The final data in the EDC will be preserved in a third-party electronic system that adheres to security requirements. No trial-related data may be destroyed without the principal investigator's (HBZ) approval.

10. Sample size

The estimation of sample size relies on data from the EAGER trial[18], which is the sole study documenting the effectiveness of acupuncture in prolonging DFS for gastric cancer patients post-surgery. In the EAGER trial, both within the intention-to-treat population, the control group exhibited a 3-year DFS rate of 54.9%, while the low-frequency EA group showed a rate of 76.5%, matching the intervention frequency used in the EAGER-2 trial, corresponding to a hazard ratio (HR) of 0.51. Therefore, assuming a median DFS of 42 months for the sham EA group and conservatively estimating an HR of 0.60 for the EA group (median DFS: 70 months), a total of 138 DFS events would be required to identify a statistically significant difference between the two groups, applying a two-sided alpha of 0.05 and a power of 85%. Anticipating an enrollment period of 36 months and a minimum follow-up of 36 months after the last participant is enrolled, 277 patients (138–139 per arm) will be required. Ultimately, a total of 346 participants will be needed to accommodate a 20% dropout rate and a 1:1 allocation ratio.

11. Statistical analysis

The Full Analysis Set (FAS) encompasses all randomized subjects based on the intention-to-treat analysis principle, with the exception of following criteria: (1) patients who either withdraw their informed consent or remain the consent but request not to be analyzed; (2) those who are incorrectly included but do not satisfy the inclusion/exclusion criteria. The Per-protocol Set (PPS) consists of patients who adhere to the treatment protocol by completing a minimum of 60% of the prescribed treatment, which is characterized by (1) at least 3 cycles of chemotherapy; (2) no less than 8 sessions of EA; (3) never receiving antitumour therapies outside the protocol, such as radiotherapy, targeted therapy , immunotherapy and interventional therapy (eg. transcatheter arterial chemoembolization, or hepatic artery infusion chemotherapy) during the study period.

DFS, FACT-Ga, mESAS, and MDASI-TCM scales score, along with OS, chemotherapy completion rates, demographics data, baseline clinical characteristics, and adverse events will be analyzed and compared in FAS. Sensitivity analysis of DFS, FACT-Ga, mESAS and MDASI-TCM scales score, OS and chemotherapy completion rates will be conducted in PPS.

The primary efficacy outcome is the difference of DFS between two groups. Patients without recurrence at the end of follow-up, or those lost to follow-up will be censored at the time of their last evaluable imaging examination from the latest date of visit. Patients without death at the end of follow-up, or those lost to follow-up will be censored at the time of the latest date of visit. Patients who have no evaluable imaging data after randomization will be censored at study day 1 unless they die within 2 visits of baseline, in which case their date of death will be used as an event[32]. Survival curves for DFS and OS will be constructed using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards regression will also be performed to calculate hazard ratios with 95% confidence intervals and to adjust for potential confounding factors.

The main secondary efficacy outcomes involve comparing the two groups regarding HRQOL and symptom burden throughout the study period. Findings from the EAGER trial[18, 33] indicate that the effect of EA on HRQOL and symptom burden is expected to be consistent across the entire intervention phase, rather than limited to specific moments. Consequently, the trajectory of HRQOL and symptom burden would be more reflective of the true effect of EA[34]. To illustrate this trajectory, standardized AUCs and average scores during treatment will be calculated using linear interpolation. The comparison of TOI, GaCS, FACT-Ga, mESAS and MDASI-TCM scores between two groups will be conducted using either Student t test or Mann–Whitney U test. Additionally, the average and the worst scores from the FACT-Ga, mESAS and MDASI-TCM scales during chemotherapy will be analyzed using the same statistical methods. Chemotherapy completion rates, demographics data, baseline clinical characteristics, and adverse events will be compared between two groups, using the χ^2 test or Fisher's exact test. Subgroup analyses will be conducted based on predefined stratification factors. Two-sided tests will be used for all analyses with a p-value <0.05 being statistically significant. Data will be analyzed using SPSS (version 16.0).

Discussion

Recurrence and metastasis after gastrectomy significantly hampers treatment effectiveness and leads to a poor prognosis[35]. The positive results of MATTERHORN for the addition of durvalumab to perioperative FLOT chemotherapy have established a new standard of neoadjuvant immunotherapy for resectable gastric or gastroesophageal junction adenocarcinoma[12]. ASTRUM-006 also demonstrated that neoadjuvant serplulimab plus SOX followed by adjuvant serplulimab significantly improved event-free survival and safety profile in resectable gastric or gastroesophageal junction adenocarcinoma with PD-L1 combined positive score (CPS)≥5[11]. However, ATTRACTION-5 revealed that nivolumab plus chemotherapy after D2 gastrectomy in stage III GC did not improve relapse-free survival, indicating the possible distinctions between neoadjuvant and adjuvant immunotherapy[10]. Current evidences do not support the use of adjuvant ICIs for stage II-III GC, except for patients who have previously received neoadjuvant ICIs[12, 36, 37], those with MSI-H/dMMR disease[6, 7, 38] or individuals with PD-L1 combined positive score (CPS)≥5[11]. In fact, these patients are not common in clinical practice. In Asia, the standard treatment for pathological stage II-III GC continues to be gastrectomy with D2 lymphadenectomy, followed by XELOX, SOX, or S-1 chemotherapy[6, 7]. Exploring treatment strategies that can prolong DFS for operable GC with adjuvant chemotherapy remains a worthwhile endeavor.

The EAGER trial has shown that acupuncture can significantly enhance DFS in GC patients undergoing adjuvant chemotherapy, with a notable increase of 21.6% in the 3-year DFS rate[18]. Research indicates that acupuncture may have both tumor-suppressing and immune-modulating properties, exerting bidirectional regulation on the quantity and activity of immune cells, altering their distribution in different tissues and organs, and strengthening the organism's defense capabilities against tumor cells[39, 40], which may contribute to prolong DFS. It is essential to conduct rigorous clinical trials aimed at DFS to confirm the effectiveness of acupuncture in conjunction with adjuvant chemotherapy and to explore the underlying mechanisms. The EAGER-2 trial will prioritize DFS as the primary outcome, while HRQOL during adjuvant chemotherapy will be a significant secondary outcome.

Building upon the EAGER trial, EAGER-2 will implement a sham-controlled framework to improve methodological value in blinding and controlling for non-specific effects[41]. A significant challenge in the EAGER-2 trial is the use of a sham control that is both physiologically inert and indistinguishable from actual treatment. The implementation of sham acupuncture involves two key aspects: point selection and needling intervention. In terms of point selection, some studies have utilized the same acupuncture points but noninsertion or limited the depth to 2 mm to prevent the activation of the *"De qi"* sensation[42, 43]. This approach aids in blinding participants familiar with acupuncture, however it still face uncertain effects of the inert control, which may fail to fully meet the traditional standards of a placebo. Many studies have adopted non-acupuncture, non-meridian points that are near the target acupoints or between two meridians[44]. It may inadvertently affect the real acupoints due to their individual locations, but can be avoided by noninsertion. Regarding needling intervention, numerous studies have employed shallow insertions (typically 2-3 mm) without eliciting *"De qi"* sensation[45, 46]. While this method effectively maintains blinding, its clinical impact should not be overlooked. A review encompassing 32 studies with 5,492 participants revealed that the insert-specific effect of sham acupuncture in randomized controlled trials accounts for 18.90% of the overall effect of acupuncture, significantly influencing the assessment of treatment outcomes[47]. The EAGER-2 trial will utilize non-penetrating sham acupuncture devices[48], which have been previously validated in acupuncture researches for their effective blinding capabilities[49-51]. These devices create a visual effect as if the needle is approaching the skin, yet they do not allow for differentiation regarding skin penetration. In summary, the sham acupuncture in the EAGER-2 trial will be conducted at non-acupuncture, non-meridian points close to the targeted acupoints, employing a blunt placebo needle and a non-insertion technique to reduce its clinical efficacy.

The acupoints prescription has been formulated based on the EAGER trial. Given that gastrointestinal symptoms are prevalent among GC patients undergoing chemotherapy, this prescription will focus on tonifying spleen-qi and stomach-qi[52], which are essential for restoring the stomach's function to receive, digest and decompose, thereby aiding in alleviating of gastrointestinal discomfort and prolong DFS. For instance, ST36, a key acupoint in this prescription, has been demonstrated to regulate gastrointestinal dysfunction[53], modulate the intestinal microecology and help repair the intestinal barrier[54] and relieve inflammation[55]. Additionally, GV20 and EX-HN3 can help regulate mental functions such as consciousness and cognition, which are important to GC patients. Back-shu Points have been selected in the EAGER trial as individual acupoints based on TCM meridian diagnostics, specifically targeting heat pain threshold at *Jing* points[56]. Among these, BL20, the Back-shu Point for the Spleen Meridian, was the most frequently used Back-shu Point in the EAGER trial, reflecting the TCM principle of selecting acupoints along meridians for specific ailments. Consequently, BL20 will be prioritized in the EAGER-2 trial over other Back-shu Points.

Acupuncture time includes needles retaining time, frequency and course. In the EAGER-2 trial, each acupuncture session is set to last for 30 minutes, aligning with the EAGER trial and most other acupuncture studies. The frequency of acupuncture in oncology treatments varies from daily to weekly[57, 58], with notable variations observed across different countries and regions. Generally, studies indicate that a higher frequency of acupuncture correlates with better outcomes[58-60]. However, findings from the EAGER trial[18] revealed that high dose EA (2-3 times weekly) did not improve HRQOL, DFS, or decrease AEs compared to low dose EA (once weekly). Therefore, once weekly acupuncture will be adopted in EAGER-2 considering to treatment adherence. Drawing long-term DFS inferences from a short-term EA intervention raises greater demands on the acupuncture course. In the EAGER-2 trial, acupuncture will be administered during the first four cycles of adjuvant chemotherapy, which is one more cycle than in the EAGER trial, aiming to enhance the effectiveness of acupuncture. Notably, a subset of patients who have received neoadjuvant chemotherapy will only undergo four cycles of adjuvant chemotherapy following surgery. Studies on acupuncture for cancers have shown that undergoing ten or more sessions can achieve the desired therapeutic benefits[58, 60, 61]. A study found that twelve acupuncture sessions over six weeks significantly alleviated joint pain associated with aromatase inhibitors in early-stage breast cancer patients[60]. Similarly, another study indicated that ten sessions of EA over eight weeks significantly improved fatigue, anxiety, and depression in breast cancer patients with aromatase inhibitor-related arthralgia[61]. Consequently, twelve sessions across four cycles will be conducted in the EAGER-2 trial. Participants will be encouraged to continue with acupuncture after completing the four cycles, as evidence indicates that a higher acupuncture sessions is associated with better therapeutic outcomes[62].

As an expansion and further validation of EAGER’s findings, this study will be the first large-sample, multi-center randomized controlled trial to assess the effectiveness of acupuncture in prolonging DFS following GC surgery. We will compare the difference in DFS between EA and SA groups ensuring a robust confirmation of acupuncture's efficacy through high-quality, evidence-based methodologies.

Abbreviations

GC Gastric cancer

ICIs Immune checkpoint inhibitors

TCM Traditional Chinese Medicine

DFS Disease-free survival

EA Electro-acupuncture

SA Sham acupuncture

CRF Case report forms

EDC Electronic Data Capture

IRC Independent review committee

HRQOL Health-related quality of life

FACT-Ga Functional Assessment of Cancer Therapy-Gastric

mESAS Modified Edmonton Symptom Assessment Scale

MDASI-TCM MD Anderson Symptom Inventory for Traditional Chinese Medicine

PWB Physical well-being subscale of FACT-Ga

SWB Social/family well-being subscale of FACT-Ga

EWB Emotional well-being subscale of FACT-Ga

FWB Functional well-being subscale of FACT-Ga

GaCS Gastric cancer subscale of FACT-Ga

TOI Trial Outcome Index, composed of PWB subscale, FWB subscale, and GaCS subscale of the FACT-Ga scores

AUC Area under curve

OS Overall survival

TRAEs Incidence of treatment-related adverse events

SAEs Serious adverse events

NCI-CTCAE National cancer institute common terminology criteria for adverse events

FAS Full Analysis Set

PPS Per-protocol Set

Declarations

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Authors' contribution

Study concept and design: HBZ, JJM and YJZ; Drafting of the manuscript: YXH, XSC and JML; Revision of the manuscript: XSC, ZYH and YDC; Statistical analysis: ZXZ and YHH; Drawing of the figures and tables: TLW; Obtained funding: HBZ. Administrative, technical, or material support: HBZ; All authors reviewed and approved the final manuscript.

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Data Availability

Not applicable. The trial results will be presented to participants, healthcare professionals, the public, and other relevant groups by reporting in trial registry and publication.

Ethics approval and consent to participate

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of the Guangdong Provincial Hospital of Traditional Chinese Medicine (approval number: BF2024-351) and registered at ClinicalTrials.gov before the first participant enrollment. The study was also approved by the Ethics Committee of sub-centers. Any important protocol modifications will be timely conveyed to sub-centers. All patients will be fully informed about the trial and given enough time to decide whether to participate in the study. All patients will be asked to sign an informed consent form if they agree to participate in the study by the research staff at sub-centers. Collection and use of participant data and biological specimens in ancillary studies will also be informed in the consent form. Each participant will receive transportation and nutrition subsidies. The trial insurance will compensate those who suffer harm from trial participation.

Trial situation

The trial is currently in the recruitment phase. This protocol version is V1.

Competing interests

The authors have no conflicts of interest to declare.

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Tables

Table 1 Schedule of assessment

Period	**screening**	**1st cycle**				**2nd cycle**				**3rd cycle**				**4th cycle**				**Follow up** [a]
Visit	0	1.1	1.2	1.3	1.4	2.1	2.2	2.3	2.4	3.1	3.2	3.3	3.4	4.1	4.2	4.3	4.4	
Timeline	-28-0	D1-21				D1-21				D1-21				D1-21				
Baseline Assessment																		
Informed consent	●																	
Randomization	●																	
Demographic data	●																	
Clinical&tumor characteristics	●																	
Credibility rating	●																●	
Intervention																		
Chemotherapy		●				●				●				●				
Usual care		●	□	□	□	●	□	□	□	●	□	□	□	●	□	□	□	
Acupuncture (EA groups)		●	●	●		●	●	●		●	●	●		●	●	●		
Sham EA (Control group)		●	●	●		●	●	●		●	●	●		●	●	●		
Safety monitoring																		
Blood test	●		□	□	●		□	□	●		□	□	●		□	□	●	
Other examinations [b]	●				●				●				●				●	
Chemotherapy side effects [c]					●				●				●				●	
Adverse events					●				●				●				●	
Assessment																		
CT/MRI [d]	●																●	●
FACT-Ga [e]	●		●				●				●				●		●	
mESAS [f]	●		●				●				●				●		●	
MDASI-TCM [g]	●		●				●				●				●		●	
Survival Follow up																		●

● Must be completed according to the protocol

□ Suggested to be completed, but not mandated.

a: 5-8 cycles of chemotherapy will be suggested, but not mandated. Follow up on cancer status and survival every 6 months.

b: Hepatic function, renal function, electrolyte test, electrocardiogram, and so on.

c: Graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, V5.0).

d: CT/MRI should be reported on the baseline, after the fourth chemo-cycle, henceforth once every 3 months for the initial 3 years, once every 6 months for years 4-5, and then annually until the conclusion of the study. Baseline image examinations include enhanced CT scan (unless contraindicated) or MRI of thorax, abdomen, pelvis, and other known or suspected tumor lesions.

e: FACT-Ga: Functional Assessment of Cancer Therapy-Gastric scale

f: mESAS: Modified Edmonton Symptom Assessment Scale

g: MDASI-TCM: MD Anderson Symptom Inventory for Traditional Chinese Medicine

Figures

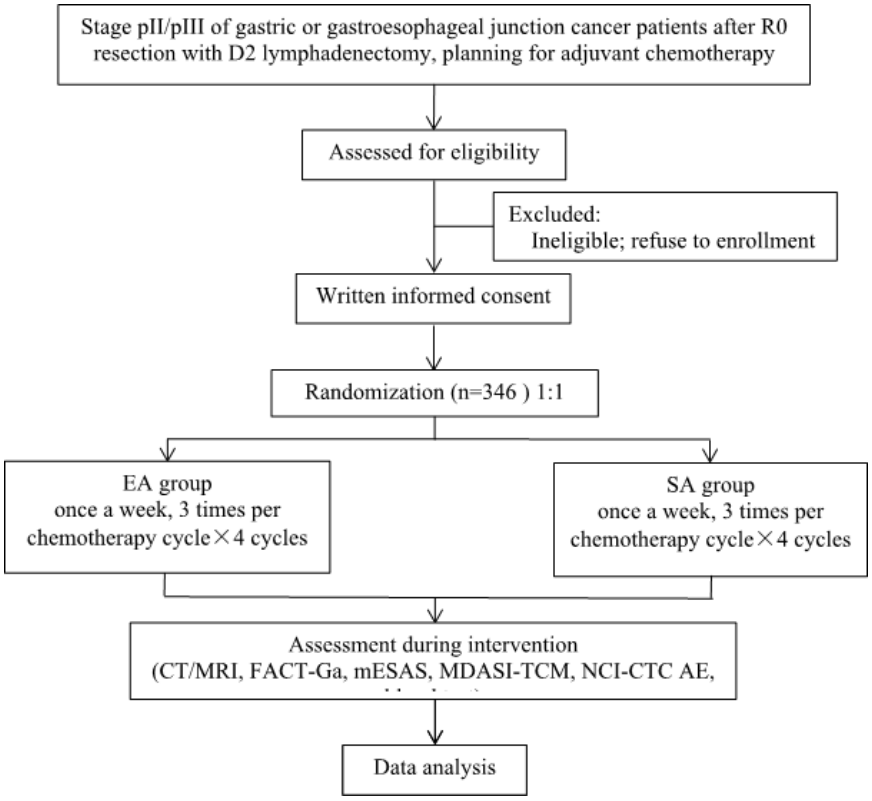


Figure 1

Trial procedure flowchart