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Neoadjuvant chemotherapy or chemoradiotherapy plus sintilimab versus neoadjuvant chemoradiotherapy for locally advanced oesophageal squamous cell carcinoma: a study protocol of a multicentre, randomised, controlled, phase III trial (SCIENCE study)

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ABSTRACT

Introduction Oesophageal squamous cell carcinoma (ESCC) is a globally challenging digestive tract malignancy with poor prognosis and limited treatment options. Early-stage ESCC is often asymptomatic, leading to a late-stage diagnosis in many cases. Neoadjuvant therapy combined with surgery is the standard treatment approach for locally advanced ESCC. In recent years, immunotherapy has shown significant efficacy in ESCC. However, various neoadjuvant treatment regimens, including chemotherapy, radiotherapy and immunotherapy, have produced inconsistent outcomes. This study aims to evaluate the efficacy and safety of neoadjuvant chemotherapy (nCT) or neoadjuvant chemoradiotherapy (nCRT) combined with immunotherapy compared with nCRT alone.

Methods and analysis This is a prospective, multicentre, randomised, controlled phase III trial enrolling 420 patients with locally advanced thoracic ESCC. Patients will be randomly assigned (1:1:1) into three groups: (A) nCT plus sintilimab, (B) nCRT plus sintilimab or (C) nCRT alone. The primary endpoints are pathological complete response and event-free survival. Secondary endpoints include the objective remission rate, disease control rate, R0 resection rate, major pathological remission rate, disease-free survival, overall survival, patient quality of life and patient-reported outcomes. Data will be analysed using both the intention-to-treat and per-protocol approaches, with multiple imputation methods for handling missing data.

Ethics and dissemination The study has been approved by the Ethics Committee for Medical Research and New Medical Technology of Sichuan Cancer Hospital (approval number: SCCHEC-02-2022-108). Written informed consent will be obtained from all participants. The findings will be disseminated through peer-reviewed journals and conference presentations.

Trial registration number NCT05244798

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, randomised, phase III clinical trial that directly compares three neoadjuvant strategies for oesophageal squamous cell carcinoma, including chemoradiotherapy with and without immunotherapy.
⇒ The trial incorporates both pathological and survival endpoints, enhancing its relevance to clinical decision-making.
⇒ Comprehensive perioperative assessment and standardised treatment protocols across centres ensure consistency and reproducibility.
⇒ The use of both intention-to-treat and per-protocol analyses strengthens the robustness of statistical conclusions.
⇒ As an open-label trial, potential bias cannot be fully excluded due to the lack of blinding.

INTRODUCTION

Data from 2022 indicate that oesophageal cancer ranks as the 11th most prevalent malignant tumour worldwide and the seventh leading cause of cancer-related mortality.[1] In China, it is the third most common malignancy in men and the fifth in women, with particularly high mortality rates in the Taihang Mountain area, southeastern Shanxi

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and the Chaoshan area.[2] Oesophageal squamous cell carcinoma (ESCC) and adenocarcinoma are the two main histological subtypes of oesophageal cancer, with ESCC being the predominant type in China, accounting for approximately 90% of cases.[3] Despite advancements in treatment, the prognosis for ESCC remains poor, with a 5-year survival rate of 15%–34%.[4]

Since early-stage ESCC typically lacks clinical symptoms, leading to a late-stage diagnosis, perioperative treatment for locally advanced ESCC has become a research focus in recent years. Based on the results of the CROSS[5] and NEOCRTEC5010[6] trials, neoadjuvant chemoradiotherapy (nCRT) has been shown to significantly improve 5-year postoperative survival rates compared with surgery alone. Consequently, both the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) guidelines recommend nCRT combined with surgery as the standard treatment protocol for ESCC. However, distant metastasis and local recurrence remain the primary causes of mortality in patients treated with nCRT followed by surgery.[7 8]

Recent studies, including Keynotes 180,[9] Keynotes 181,[10] ATTRACTION-1[11] and ATTRACTION-3,[12] have demonstrated that chemotherapy combined with immunotherapy yields favourable outcomes in advanced ESCC. Furthermore, the CheckMate-577 trial[13] has shown that postoperative adjuvant therapy with PD-1 inhibitors following nCRT significantly prolongs progression-free survival. As a result, multiple phase II single-arm clinical trials, including those conducted at our centre,[14] have demonstrated the feasibility and therapeutic promise of integrating immunotherapy into neoadjuvant regimens for locally advanced ESCC. However, these studies exhibit significant variability in treatment protocols and outcomes and lack direct comparison with the current standard treatment.[15]

Given the groundbreaking potential of immunotherapy in advanced ESCC and the remarkable survival benefits demonstrated by PD-1 inhibitors in the postoperative setting, there is a strong rationale for incorporating immunotherapy into neoadjuvant regimens. Combining immune checkpoint inhibitors (ICIs) with neoadjuvant chemotherapy (nCT) or nCRT not only strives to amplify therapeutic efficacy and elevate pCR rates but also strategically addresses recurrence risks, ultimately prolonging survival outcomes. The immunomodulatory properties of chemotherapy and radiotherapy may create a favourable tumour microenvironment, potentially augmenting the efficacy of PD-1 inhibitors. Although numerous phase II trials[14–16] have demonstrated the feasibility of neoadjuvant chemoimmunotherapy and nCRT combined with immunotherapy in ESCC, robust comparative data directly evaluating different neoadjuvant combination strategies remain limited. This study aims to address this gap by conducting a multicentre, randomised phase III trial comparing nCT or nCRT combined with immunotherapy versus nCRT alone in patients with locally advanced ESCC. The findings will provide critical evidence on whether the integration of immunotherapy with standard neoadjuvant treatment can optimise clinical outcomes in ESCC patients.

METHODS

Study design and setting

This study is a prospective, multicentre, randomised, controlled phase III clinical trial. A total of 420 patients with locally advanced thoracic ESCC will be recruited. Eligible participants will be randomly assigned in a 1:1:1 ratio to one of three groups: nCT combined with sintilimab (group A), nCRT combined with sintilimab (group B) or nCRT (group C) (figure 1).

Group A (nCT+sintilimab): patients will receive neoadjuvant treatment consisting of sintilimab (administered on day 1) combined with chemotherapy (TP regimen: albumin-bound paclitaxel+carboplatin, administered on day 1) for two cycles, with each cycle lasting 3 weeks (Q3W). Surgery will be performed 6–8 weeks after completing neoadjuvant therapy. Postoperative adjuvant treatment will be determined by the investigator according to ESCC treatment guidelines.

Group B (nCRT+sintilimab): patients will receive neoadjuvant treatment consisting of sintilimab (administered on day 1) combined with concurrent chemoradiotherapy. The chemotherapy regimen will follow the TP protocol (albumin-bound paclitaxel+carboplatin, administered on day 1) for two cycles, each cycle lasting 3 weeks (Q3W). Radiotherapy will be administered according to an intensity-modulated radiotherapy (IMRT) plan with a total dose of 41.4 Gy, divided into 23 fractions, 5 days per week. Surgery will be performed 6–8 weeks after completing neoadjuvant therapy. Postoperative adjuvant treatment will be determined by the investigator according to ESCC treatment guidelines.

Group C (nCRT): patients will receive neoadjuvant treatment consisting of concurrent chemoradiotherapy. The chemotherapy regimen will follow the TP protocol (albumin-bound paclitaxel+carboplatin, administered on day 1) for two cycles, each cycle lasting 3 weeks (Q3W). Radiotherapy will be administered according to an IMRT plan with a total dose of 41.4 Gy, divided into 23 fractions, 5 days per week. Surgery will be performed 6–8 weeks after completing neoadjuvant therapy. Postoperative adjuvant treatment will be determined by the investigator according to ESCC treatment guidelines.

Treatment regimens

Chemotherapy

Carboplatin: administered intravenously on day 1 of each cycle at an area under the curve of 4–5. Each cycle lasts 21 days, with a total of two cycles.

Albumin-bound paclitaxel: administered intravenously on day 1 of each cycle at a dose of 220–260 mg/m². Each cycle lasts 21 days, with a total of two cycles.

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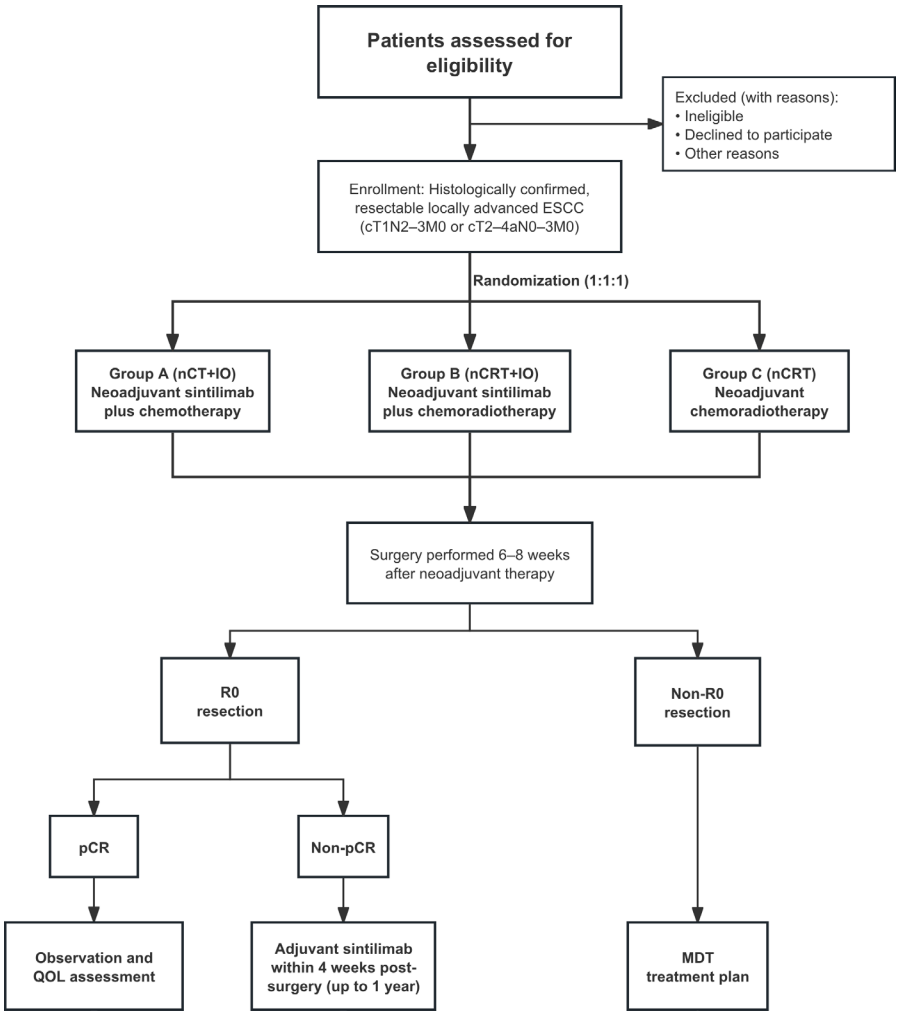

Figure 1 CONSORT flow diagram of the SCIENCE study. CONSORT, Consolidated Standards of Reporting Trials; nCRT, neoadjuvant chemoradiotherapy; nCT, neoadjuvant chemotherapy; ESCC, oesophageal squamous cell carcinoma; IO, immunotherapy; pCR, pathological complete response; MDT, multidisciplinary team; QOL, quality of life.

Immunotherapy

Patients in groups A and B will receive two cycles of preoperative sintilimab (200 mg/day, administered on day 1), repeated every 3 weeks.

Radiotherapy

A total radiation dose of 41.4 Gy will be delivered in 23 fractions (1.8 Gy per session, five sessions per week). Standardised IMRT or image-guided radiotherapy will be used for all patients, utilising an accelerator beam energy of ≥6 MV. Efforts will be made to ensure that radiotherapy remains uninterrupted during concurrent treatment. If a patient experiences severe oesophagitis requiring chemotherapy interruption, radiotherapy may continue if the investigator deems it safe with supportive care.

CT simulation and target volume delineation: all patients will undergo contrast-enhanced CT simulation scanning with a slice thickness of 3 mm in the supine position. Gross tumour volume (GTV) is defined as the primary oesophageal tumour (GTVt) and locoregional metastatic lymph nodes (GTVn) identified through clinical examination, contrast-enhanced CT, esophagography, endoscopy and positron emission tomography (PET/CT). Clinical target volume (CTV): CTVt (primary tumour): includes a 3 cm margin cranio-caudally and a 0.5–0.6 cm radial margin from GTVt, adjusted based on anatomical boundaries (eg, heart, lungs and bones). CTVn (lymph nodes): includes GTVn plus a 0.5 cm margin in all directions, adjusted based on anatomical boundaries. Planning target volume: applied according to institutional protocols, typically 5–10 mm expansion. Organs at risk: delineated structures include the heart, lungs, trachea, bronchi, spinal cord, thyroid gland, liver and kidneys.

Surgical procedures

Patients will undergo preoperative imaging assessment and surgical eligibility evaluation 6–8 weeks after neoadjuvant therapy. Minimally invasive oesophagectomy is recommended and should ideally be performed 6 weeks postneoadjuvant therapy, but no later than 8 weeks, provided laboratory parameters such as white blood cells, platelets, liver and kidney function return to normal. For middle and lower ESCC, a two-field lymph node dissection will be performed. For upper ESCC, a three-field lymph

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node dissection is recommended. A minimum of 20 lymph nodes should be pathologically examined. Thoracoscopic, open thoracotomy and hybrid oesophagectomies are acceptable.

Study endpoints

The primary outcomes of the study are the pCR rate and event-free survival (EFS). pCR is defined as the absence of residual tumour cells in both the primary site and the resected lymph nodes of the surgical specimens. The pathological results of pCR patients require centralised review and confirmation to ensure accuracy and consistency. EFS is defined as the time from randomisation to any of the following events: disease progression precluding surgery, local or distant recurrence or death from any cause.

The secondary outcomes include the objective remission rate (ORR), disease control rate (DCR), R0 resection rate, major pathological remission (MPR) rate, disease-free survival (DFS), overall survival (OS), patient quality of life and patient-reported outcomes. ORR is defined as the proportion of patients who achieve either a complete response (CR) or a partial response (PR), based on RECIST V1.1 criteria. DCR is the proportion of patients who achieve CR, PR or stable disease (SD) at 2 months postrandomisation. R0 resection is defined as microscopically margin-negative resections. MPR is defined as ≤10% residual tumour cells in surgical specimens after neoadjuvant treatment. DFS is the time from randomisation to disease progression or recurrence, and OS is the time from diagnosis to death from any cause. The incidence of adverse events (AEs) is determined as the proportion of participants experiencing treatment-related AEs, assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (CTCAE V.4.0). Postoperative complications were evaluated using the Oesophageal Complications Consensus Group criteria.

Participants

The study involves patients with ESCC diagnosed at the Sichuan Cancer Hospital, which leads a collaboration with 10 hospitals. These patients undergo a thorough diagnostic process, including physical examination, gastroscopy, endoscopic ultrasound, contrast-enhanced CT scans of the neck, chest and abdomen, cervical and abdominal ultrasound, oesophagography, electrocardiography and pulmonary function tests. If agreed on by the patient, PET/CT is also performed. All patients receive pretreatment clinical staging according to the eighth edition of the AJCC/UICC TNM classification system for cancer.[17] Written informed consent is obtained from all patients before recruitment.

Inclusion criteria

1. Aged between 18 and 75 years, both sexes.
2. Histologically confirmed locally advanced (cT1N2-3M0 or cT2-4aN0-3M0) thoracic ESCC based on the eighth AJCC/UICC-TNM staging system.
3. Cervical contrast-enhanced CT shows no suspicious metastatic lymph nodes and no evidence of systemic metastasis on imaging.
4. Expected to achieve R0 resection.
5. Eastern Cooperative Oncology Group performance status of 0 or 1.
6. No previous antitumour therapy for ESCC.
7. Measurable lesions according to RECIST V.1.1 criteria.
8. No contraindications to surgery based on the evaluation of various organ functions.
9. Laboratory test results confirming adequate bone marrow, liver and kidney function:
   - Haemoglobin ≥90 g/L.
   - White blood cell count≥lower limit of normal.
   - Absolute neutrophil count≥1.5×10^9/L.
   - Platelet count≥100×10^9/L.
   - Total bilirubin≤1.5 × upper limit of normal (ULN).
   - Alanine aminotransferase and aspartate aminotransferase≤2.5 × ULN.
   - Prothrombin time≤16 s and international normalised ratio≤1.5 × ULN.
   - Serum creatinine≤1.5 × ULN or creatinine clearance≥50 mL/min (Cockcroft-Gault formula).
10. Fertile women must agree to use effective contraception and have a negative serum pregnancy test before enrolment; men must agree to use effective contraception.
11. Signed informed consent obtained from all participants before enrolment.

Exclusion criteria: patients will be excluded if they meet any of the following criteria

1. Diagnosis of other malignant tumours within 5 years before randomisation.
2. High bleeding tendency, history of gastrointestinal bleeding, coagulopathy or ongoing thrombolysis or anticoagulant therapy.
3. Severe cardiovascular and cerebrovascular diseases.
4. Interstitial lung disease or pneumonia requiring steroid treatment at enrolment.
5. Active tuberculosis or history of antituberculosis therapy in the past.
6. Asthma requiring intermittent medical interventions.
7. Infectious diseases requiring systemic treatment.
8. Severe unhealed wounds, active ulcers or untreated fractures.
9. Other inoperable conditions.
10. Previous surgeries that preclude the use of the stomach for reconstruction in this surgery.
11. Systemic steroid therapy or other immunosuppressive agents within 2 weeks before randomisation.
12. Severe allergy to chemotherapy drugs or any monoclonal antibody.
13. Active autoimmune disease requiring systemic treatment in the past 2 years.
14. History of organ transplantation.

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15. HBV DNA>500 IU/mL for HBsAg (+) and/or HBcAb (+).
16. HCV RNA>10^3 copies/mL and/or HCV antibody positive.
17. HIV coinfection.
18. Other conditions deemed unsuitable by the investigator.

Follow-up

The primary endpoints will be analysed 3 months after the surgical treatment of the last recruited patient. During the follow-up period, contrast-enhanced chest CT and cervical and abdominal ultrasound will be performed to monitor for recurrence or metastasis. Follow-up assessments for disease recurrence or death will be conducted every 3 months for the first 2 years, and every 6 months from the third to the fifth year.

Sample size calculation

The sample size calculation was conducted to ensure sufficient statistical power to detect meaningful differences among the treatment arms. Based on prior clinical studies and expected pCR rates, we assumed: neoadjuvant chemoradiotherapy plus immunotherapy (nCRIT): 56.5%, nCT plus immunotherapy (nCIT): 18.8%, nCRT: 35%. To achieve a power of 90% with a two-sided alpha of 0.02 for the primary endpoint (pCR), a total of 140 patients per group was calculated, considering a dropout rate of 15%. For EFS, assuming an HR of 0.65, a total of 195 EFS events are required to maintain 80% power at a 0.03 significance level.

To ensure the robustness of the sample size estimation, an independent statistician has reviewed and validated the methodology. The study is designed to balance feasibility with adequate statistical power to detect clinically meaningful differences.

Statistical analysis

The primary endpoints, including the pCR rate and EFS, and secondary endpoints, such as OS, ORR, MPR and DFS, will be analysed using appropriate statistical methods. The pCR rate will be compared between groups using the χ^2 test or Fisher's exact test, as appropriate. EFS, DFS and OS will be estimated using the Kaplan-Meier method, with differences assessed by the log-rank test. Cox proportional hazards regression models will be used to calculate HRs with 95% CIs, adjusting for potential confounders.

Descriptive statistics will be used for baseline characteristics and outcome measures. Continuous variables will be presented as mean with SD or median with IQR, depending on data distribution. Categorical variables will be summarised as frequencies with percentages. Differences between groups will be assessed using χ^2 tests for categorical variables and one-way analysis of variance or Kruskal-Wallis tests for continuous variables, as appropriate. A two-sided p-value of <0.05 will be considered statistically significant.

OS, 12 month, 36 month and 60 month survival rates, as well as median survival, will be estimated using Kaplan-Meier methods. Multivariate Cox proportional hazards regression models will be used to further analyse survival outcomes.

Both intention-to-treat (ITT) and per-protocol (PP) analyses will be performed to evaluate the robustness of the findings. The primary analysis will be conducted using the ITT analysis set, including all randomised participants regardless of treatment adherence. The PP analysis set will include only participants who complete the assigned treatment protocol without major deviations. Missing data will be handled using multiple imputation methods, assuming data are missing at random. Sensitivity analyses will be conducted to assess the impact of missing data on the primary and secondary outcomes. All statistical analyses will be performed using R software or equivalent statistical software.

Two interim analyses will be conducted for futility assessment, scheduled at one-third and two-thirds of the total planned enrolment. Stopping rules and the control of type I error for multiple comparisons are prespecified in the statistical analysis plan to maintain the overall type I error rate at the prespecified level, with the use of the Lan–DeMets alpha spending function with O'Brien–Fleming boundaries. The independent data monitoring committee will review the interim results and provide recommendations on whether the trial should continue, be modified, or be terminated early.

Monitoring

Patient safety, study progress, and data integrity will be evaluated every 3 months by the Good Clinical Practice (GCP) board and the Ethics Committee for Medical Research and New Medical Technology of Sichuan Cancer Hospital. The principal investigators (PIs) are responsible for the study's design and execution, ensuring compliance with regulatory and ethical guidelines.

Participating institutions

The study will be conducted in collaboration with the following institutions: Sichuan Cancer Hospital (Lead Institution), Peking University Cancer Hospital and Institute, Tianjin Medical University Cancer Institute and Hospital, Hebei Medical University Fourth Hospital, Anhui Provincial Hospital, The First Affiliated Hospital with Nanjing Medical University, Anyang Tumour Hospital and Shantou Central Hospital. Each institution is represented by a PI responsible for overseeing study implementation at their respective sites.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this research. The study was designed based on existing clinical guidelines and expert consensus. However, study results will be shared with patient advocacy groups and relevant stakeholders to ensure broader dissemination and potential

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impact on future treatment strategies. Future studies may incorporate direct patient and public involvement in research planning and decision-making processes.

ETHICS AND DISSEMINATION

This study has been approved by the Ethics Committee for Medical Research and New Medical Technology of Sichuan Cancer Hospital (approval number: SCCHEC-02-2022-108). Written informed consent will be obtained from all participants before enrolment. The trial will be conducted in accordance with the principles of the Declaration of Helsinki and GCP guidelines.

Study findings will be disseminated through peer-reviewed journal publications and presentations at national and international conferences. Additionally, study findings will be shared with relevant clinical and research communities to contribute to the optimisation of neoadjuvant treatment strategies for locally advanced ESCC. No identifying patient information will be disclosed in any publication or presentation.

Study data will be managed in compliance with institutional and regulatory policies, ensuring participant confidentiality and data integrity. Any significant protocol amendments will be submitted for ethical approval and communicated appropriately to investigators and participants.

DISCUSSION

According to a comprehensive overview of cancer incidence and mortality rates in China for the year 2022, the incidence rate of oesophageal cancer was 8.32 per 100 000 people, with a mortality rate of 6.68 per 100 000 people.[1] Oesophageal cancer incidence and mortality rates demonstrate a gender disparity, with men having an incidence rate of 13.09 per 100 000 and a mortality rate of 10.70 per 100 000, while women have an incidence rate of 3.78 per 100 000 and a mortality rate of 2.92 per 100 000.[18]

NCRT followed by surgery has become the standard approach for treating locally advanced oesophageal cancer based on evidence from trials such as CROSS[5] and NEOCRTEC5010.[6] Both trials demonstrated that nCRT improves survival and pCR rates. However, these studies also reported high rates of distant metastasis following nCRT and surgery for ESCC, with rates of 39% and 23.9%, respectively.[5 6] This highlights the urgent need for more effective systemic treatments to address both local and distant recurrences, which occur in up to 57.1% of cases, with locoregional recurrences being the most common.[19 20] With the advancement of immunotherapy in metastatic ESCC,[12] increasing efforts are being made to replicate its success in the neoadjuvant setting for resectable ESCC.

Beyond standard nCRT, many studies have explored the efficacy of nCT combined with immunotherapy for ESCC. A pooled analysis of 17 trials involving 455 patients assessed the efficacy and safety of neoadjuvant immunotherapy for resectable oesophageal or gastro-oesophageal junction carcinoma.[21] The analysis found no significant improvement in pCR rates and an increased risk of severe AEs. However, another meta-analysis of 21 trials with 759 patients showed better outcomes in MPR (52.0%) and a lower incidence of treatment-related adverse events.[22] Despite these promising results, the meta-analysis failed to show significant improvements in pCR rates or recurrence reduction.

Early-phase clinical studies reveal that immunotherapy combined with chemotherapy or radiotherapy has synergistic effects. Available clinical data on ICIs with radiotherapy for preoperative ESCC treatment are encouraging. A pooled analysis of 925 patients from 36 studies on neoadjuvant immunotherapy plus chemoradiotherapy (NICRT) or chemotherapy (NICT) reported a notably high R0 resection rate of 99%, with pCR rates of 38% in the NICRT group compared with 28% in the NICT group. The MPR rate was 58% overall, with NICRT at 67% and NICT at 57%.[23] Several trials have further explored NICRT in ESCC, including those evaluating camrelizumab with radiotherapy,[24] tislelizumab after chemoradiotherapy,[25] comparisons of nCRT plus surgery versus definitive chemoradiotherapy[26] and the use of simultaneous integrated boost-IMRT with or without concurrent chemotherapy.[27]

Given the expanding role of PD-1 inhibitors and their demonstrated survival benefits, integrating immunotherapy into neoadjuvant treatment for ESCC appears to be a promising strategy. The immune-modulating effects of chemotherapy and radiotherapy may enhance the efficacy of PD-1 inhibitors by improving the tumour microenvironment. However, despite encouraging findings from phase II trials, large-scale randomised controlled trials directly evaluating the comparative effectiveness of diverse neoadjuvant therapeutic strategies in ESCC remain conspicuously absent.

To bridge this critical gap, we meticulously designed a multicentre, randomised phase III trial that directly compares three prevalent clinical approaches: nCT or nCRT combined with immunotherapy, and standard nCRT alone. This study hypothesises that the addition of immunotherapy to neoadjuvant therapy will yield superior pCR rates and enhance survival outcomes for patients with locally advanced, operable ESCC. Patient recruitment for this trial began in November 2022, with a target enrolment of 420 patients across approximately 10 hospitals in China over the next 4–5 years. The findings from this study will provide critical evidence on whether immunotherapy can be effectively integrated into standard neoadjuvant treatment strategies to optimise clinical outcomes in ESCC.

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Contributors WH, JL, YH and XL conceptualised the study. WH, HB and JL drafted the manuscript. WH, JL and XL were responsible for trial registration at the Clinical Trial website. PT, TH, HZ, WX, LP, GL, KW, QF, YQ, LL, XZ, HQ, YC, YZ, WX, YH and XL assisted in patient enrolment. WH, JL and XL contributed to the discussion and English language revisions. YH and XL provided treatment guidance and modifications. WH, HB and JL managed research data. XL is responsible for the overall content as guarantor. All authors contributed to the article and approved the final version. After completing my manuscript, I used ChatGPT 4o to help with language polishing and editing.

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Disclaimer Sintilimab was provided free of charge by Innovent Company, which had no competing interests in this study. The company did not participate in any aspect of the research, including study design, data collection, data management, statistical analysis, result interpretation, manuscript preparation or the decision to submit the findings for publication. All aspects of the study were conducted independently by the investigators.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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