Study Protocol

Electronic patient-reported outcome-based surveillance system to evaluate safety and efficacy of preoperative immunochemotherapy with or without short-term chemoradiation in patients with esophageal squamous cell carcinoma (ePRO-PICCRT): protocol for a prospective, single-arm, phase II study

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Background: Radiation-associated adverse events (ADEs) in patients with esophageal squamous cell carcinoma (ESCC) remain a problem. Recent research has focused on reducing radiation-associated ADEs while maintaining efficacy, particularly through the combination of immune checkpoint inhibitors (ICIs) with chemotherapy. Patient-reported outcomes (PROs) have also emerged as reliable measures for monitoring treatment effectiveness and quality of life (QoL). This trial aims to investigate the feasibility of using patient-reported dysphagia relief to assess pathological response following neoadjuvant immunochemotherapy, as well as the safety and efficacy of neoadjuvant immunochemotherapy combined with short-course radiotherapy for patients with locally advanced ESCC.

Methods: This study is designed as a prospective, single-arm, phase II study. Eligible ESCC patients will be invited to participate in this study. All participants will receive paclitaxel (albumin-bound) (260 mg/m^2, day 1), carboplatin [area under the curve (AUC) 5; 5 mg/mL/min, day 1] or cisplatin [60 mg/m^2, intravenous drip (ivdrip), day 1], and tislelizumab (200 mg, day 1) in the first treatment cycle. Early remission of dysphagia is defined as relief greater than 70% according to the dysphagia symptom score in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire esophagus-specific questionnaire (EORTC OES-18). The early remission group (Group A) will continue with the same regimen for two treatment cycles. The latent remission group will continue with one treatment cycle followed by neoadjuvant immunochemotherapy combined with short-course radiotherapy (radiotherapy 30 Gy/10 F). The primary objective is the pathological complete response (pCR) rate. Research data collection, storage, and management will be conducted in a web-based Real-World-Data Management Platform (RWDMP). Longitudinal data will be conducted by a linear mixed model with treatment effects, baseline factors influencing the endpoint as fixed effects, and the center as a random effect.

Discussion: This study will provide evidence for using patient-reported dysphagia relief to evaluate pathological response after neoadjuvant immunochemotherapy in early remission (Group A) and to evaluate the safety and efficacy of combining immunochemotherapy with short-course radiotherapy in latent remission (Group B) among patients with ESCC. Limitations include the single-arm study design, small sample size, and the need for further exploration of the specific mechanism and mediator of early dysphagia remission's effect on immunochemotherapy effectiveness.

Trial Registration: This study is registered at Clinicaltrials.gov (NCT05596890).

Keywords: Esophageal squamous cell carcinoma (ESCC); electronic patient-reported outcome (electronic PRO); immunochemotherapy; short-course radiotherapy

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Introduction

Background

Since the release of NEOCRTEC5010 and CROSS results, neoadjuvant chemoradiotherapy has become the standard-of-care for locally advanced esophageal cancer (EC). It was reported that in the chemoradiotherapy cohort, the pathological complete response (pCR) reached 43.2% with a 5-year overall survival (OS) rate of 59.9% (1,2). Despite the satisfying efficacy, nearly 40% of patients had radiation-associated adverse events (ADEs) (2). Hence, substantial efforts have been made to reduce ADE of radiation and find alternative regimens with comparable efficacy.

Rationale and knowledge gap

Currently, a major research focus is "de-radiotherapy". Several phase III studies comparing the efficacy and safety of neoadjuvant chemotherapy versus chemoradiotherapy showed that the addition of radiotherapy to neoadjuvant chemotherapy did not result in more survival benefits for patients with esophageal squamous cell carcinoma (ESCC) (3-5). Recently, the JCOG1109 NExT study, a 3-arm phase III trial demonstrated that the 3-year OS in neoadjuvant chemotherapy was comparable to that in neoadjuvant chemoradiotherapy (4). Based on the above research evidence, neoadjuvant chemotherapy is increasingly appreciated. With the advances in tumor immunotherapy, immune checkpoint inhibitors (ICIs) such as programmed cell death-1 (PD-1) inhibitors combined with chemotherapy in neoadjuvant settings have been proven to be more effective than chemotherapy alone (6), with a pCR rate of 41.4% (7).

Another important approach to reduce radiation-associated ADEs is adopting short-course radiotherapy combinations. The neoadjuvant hypo-fractionated radiotherapy plus chemotherapy has been demonstrated as an effective and safe alternative which brings about comparative OS with conventionally fractioned radiotherapy (8). Moreover, the combination of short-course neoadjuvant chemoradiotherapy and immunotherapy for ESCC suggests a beneficial outcome. Jiang *et al.* reported that 55% of patients who received short-course chemoradiotherapy (30 Gy: 3 Gy × 10 F) plus toripalimab achieved complete pathological response (9).

Patient-reported outcomes (PROs) refer to the patient's self-assessment of his/her own health and treatment outcomes without interpretation by a healthcare professional (10,11). It is a new outcome measure recommended by the U.S. Food and Drug Administration. It has been used in clinical research, drug approval, and quality assessment of healthcare services in Europe and the United States because of its reliability, sensitivity, and ease of use in measuring patients' daily functioning and symptoms (12). Unlike biological and other clinical outcome indicators, patients' functional status of symptoms is more accurately assessed by themselves than by healthcare professionals. Recent large-scale clinical trials have shown that the use of PROs-based symptom monitoring and alerts during chemotherapy courses not only improves the quality of life (QoL) but also significantly prolongs cancer patients' survival (13-15). It has been suggested that early remission

of dysphagia, the chief EC-associated symptom during chemotherapy may be a predictor of effective outcome assessment (16). Clinically, relief of dysphagia is often observed 2 to 3 weeks after the first course of radiotherapy/chemotherapy in patients with locally advanced EC. In the immunotherapy cohort, this phenomenon occurs even more frequently (17). Previously, we identified that early and persistent relief of patient-reported dysphagia is a significant predictor for the pathological response of ESCC treated with immunochemotherapy. Furthermore, we suggested that long-term PROs could be a simple, affordable, and non-invasive method of predicting tumor responses to neoadjuvant immunochemotherapy (10,18). It may be possible to protect patients from the harm caused by preoperative radiation and further enhance the prognosis by identifying early ESCC responders to neoadjuvant immunochemotherapy through dynamically monitoring PROs.

Objective

This prospective, explorative, phase II study aims to investigate (I) the feasibility of using patient-reported dysphagia relief to assess pathological response following neoadjuvant immunochemotherapy; (II) the safety and efficacy of neoadjuvant immunochemotherapy combined with short-course radiotherapy for patients with locally advanced ESCC. We hypothesize that (I) it will be feasible to utilize patient-reported dysphagia relief to assess pathological response following neoadjuvant immunochemotherapy in patients with ESCC; (II) neoadjuvant immunochemotherapy combined with short-course radiotherapy will not have worse safety and efficacy compared to that of current standard-of-care conventional chemoradiotherapy. We present this article in accordance with the SPIRIT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-274/rc).

Methods

Study design

This is a multicenter, prospective cohort study including patients with locally advanced ESCC receiving neoadjuvant treatment. The results of this cohort study will be reported according to the guidelines of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for cohort study (19). The inclusion and exclusion criteria for this study are shown below. The flowchart of the study design is presented in *Figure 1*.

Study setting/location

The study is initiated by Guangdong Provincial People's Hospital and designed to be carried out at four hospitals in China. The participating centers include the First Affiliated Hospital of Shantou University Medical College, the First Affiliated Hospital of Guangdong Pharmaceutical University, and the General Hospital of Southern Theater Command. The actual initiation date is November 30, 2022 and the primary completion date is expected to be on September 30, 2025.

Inclusion criteria

(I) Pathologically confirmed ESCC;
(II) Potentially resectable ESCC at first diagnosis (cT1–4aN1–2M0, cT3–T4aN0M0);
(III) Anti-tumor treatment-naive;
(IV) Expected life span >6 months;
(V) Aged 18–75 years old;
(VI) Adequate organ functions;
(VII) Having an Eastern Cooperative Oncology Group performance scale (ECOG PS) of 0–2;
(VIII) Participants are fully informed about the whole study and are willing to sign the informed consent.

Exclusion criteria

(I) Previous history of thoracic surgery or radiation;
(II) Cervical or multi-origin EC;
(III) Known or suspected experimental drug allergy;
(IV) Pregnant or lactating women;
(V) Esophagomediastianl fistula or esophagotracheal fistula;
(VI) Peripheral neuropathy;
(VII) Previous cancer history other than EC;
(VIII) Severe organ function deterioration that can not tolerate neoadjuvant therapy;
(IX) Previous autoimmune diseases or immunodeficiency disorders;
(X) Diabetic history >10 years or poor glycemic control;
(XI) Interstitial pulmonary disease, non-infectious pulmonitis;
(XII) Active type B hepatitis or type C hepatitis;

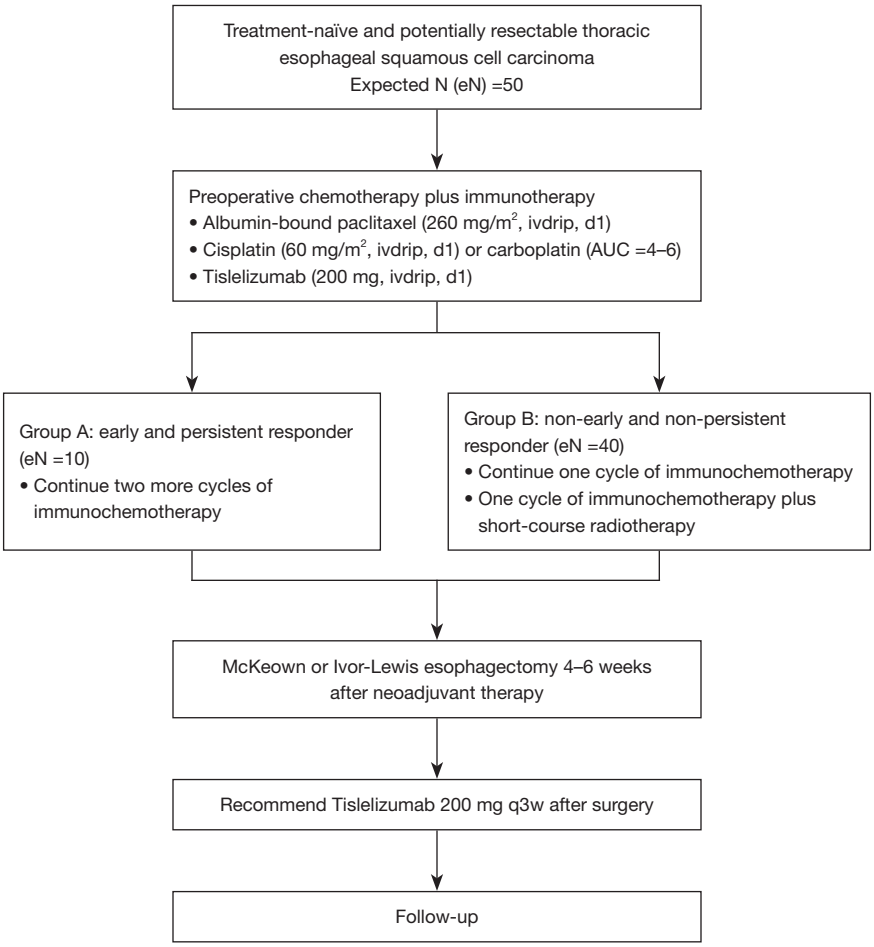

Figure 1 Flowchart of study design. ivdrip, intravenous drip; d1, day 1; AUC, area under the curve; q3w, every 3 weeks.

(XIII) Any other conditions that may affect patients' safety and compliance.

Sample size

Participants are divided into two groups based on the relief degree of symptom score during treatment. The ePRO-PICCRT trial is powered for its primary endpoint: pCR rate. A recent research in targeted patients treated with a combination of neoadjuvant immunochemotherapy reported that 25% of patients achieved pCR. We hypothesized the ratio of the early remission group (Group A) to the latent remission group (Group B) is 1:4. For sample size calculation, the pCR rate of 93% in Group A and 45% in Group B is deemed achievable. The 93% complete response (CR) rate in Group A is derived from our previous pilot study. In the pilot study, we prospectively followed up 128 patients with locally advanced ESCC using the EORTC OES-18 scale. We tracked patient-reported dysphagia symptoms at multiple time points (initial diagnosis, after the 1st, 2nd, and 3rd treatment cycles, preoperative visit, and 1-month post-surgery). The dysphagia symptoms were evaluated using three specific questions from the EORTC OES-18 scale: could you eat solid food? Could you eat liquidized or soft food? Could you eat liquidized or soft food. The symptom relief was calculated using the formula:

$$\Delta\text{Symptom relief} = \frac{\text{`score at the end of first cycle'} - \text{`score at baseline'}}{\text{`score at baseline'}} \times 100(\%) \quad [1]$$

Using the receiver operating characteristic (ROC) curve, we determined a cut-off value of 70% for symptom relief. Patients with symptom relief greater than 70% were defined as having early remission (Group A), while others were classified as having latent remission (Group B). Our study observed that 93.3% of the patients in the early remission group achieved pCR. In contrast, 97.7% of patients in the latent remission group did not achieve pCR (P<0.001). Further analysis showed that early symptom relief was a significant independent predictor for pCR, with a sensitivity of 97.9%, specificity of 93.3%, positive predictive value of 98.0%, and negative predictive value of 93.0%. The ROC curve analysis indicated an area under the curve (AUC) value of 0.954 [95% confidence interval (CI): 0.876–1.000, P<0.001]. Considering a prespecified one-sided α=0.05 and a type II error rate β=0.20 (statistical power =80%), a sample size of 36 in Group B is defined based on the group sequential test for two proportions. Taking drop-out data of 10% into account, this renders a total study population of 50 patients. A sample size of 10 and 40 are identified in Group A and Group B.

Outcomes measures

Primary outcome

The primary outcome of this study is the pCR rate defined as no signs of cancer in tissue samples removed during surgery or biopsy after immunochemotherapy with short-course radiotherapy.

Secondary outcome

(I) The feasibility of ePRO-based classification in Group A is defined as a pCR rate higher than 93% and in Group B higher than 45%.

(II) Objective response rate (ORR): CR and partial response (PR) are defined by immune Response Evaluation Criteria in Solid Tumors (iRECIST) criteria (20). CR, all target lesions disappeared and no new lesion appeared, and the short diameter of lymph nodes is less than 1 cm, which are maintained for 4 weeks or until the time of surgery. PR, ≥30% decrease in tumor size compared to the baseline measurement of the largest diameter.

(III) QoL scores: QoL scores of symptom relief after the first cycle of immunochemotherapy; scores of the EORTC OES-18 and QLQ-C30 before treatment (at baseline), from the start of treatment until the end of each cycle before surgery, and every 3 months after surgery.

(IV) Safety: measured by the number of participants with Grade 3 or 4 ADEs as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

(V) MPR: major pathologic remission, residual tumor of less than or equal to 10%.

(VI) R0 resection rate: the rate of no tumor cells within 1mm of the resection margin.

(VII) Event-free survival (EFS): time from the start of recruiting to the date of first progression (local recurrence of tumor or distant metastasis) or death from any cause, whichever occurred first.

(VIII) OS: time between the start of recruiting and death due to any cause or end of the follow-up.

(IX) Progression-free survival (PFS): time between the start of recruiting and the time of disease progression or death due to any cause.

Other data

Demographics, clinical characteristics, perioperative indicators, and information on drugs combination will also be collected.

Recruitment of participants

Participant recruitment will be carried out before treatment by clinicians in the clinic. The completed medical history and physical examinations will be required within 7–10 days before the treatment (including weight, ECOG PS, routine examinations, QoL, and Nutritional Risk Screening 2002). Participants will be screened by the inclusion and exclusion criteria. Preoperative chemotherapy combined with immunotherapy will be administered: paclitaxel (albumin-bound) (260 mg/m^2, day 1), carboplatin (AUC 5; 5 mg/mL/min, day 1) or cisplatin [60 mg/m^2, intravenous drip (ivdrip), day 1], and tislelizumab (200 mg, day 1). During the first cycle of immunochemotherapy, the evaluation of QoL by EORTC OES-18 and QLQ-C30 scales, and images by PET-CT or enhanced CT will be performed. Patients will be divided into two groups (Group A and Group B) according to the dysphagia symptom alleviation after the first cycle of immunochemotherapy.

During the second and third treatment cycles, Group A will continue the same neoadjuvant immunochemotherapy regimen for two treatment cycles. In the case of Group B, the same neoadjuvant immunochemotherapy regimen

will be administered in the second cycle, following with neoadjuvant immunotherapy (tislelizumab, 200 mg, day 2) plus chemotherapy (albumin-bound paclitaxel, 60 mg/m^2, days 1, 8, 15), and carboplatin (AUC 2; 2 mg/mL/min, days 1, 8, 15) or cisplatin (60 mg/m^2, ivdrip, day 1) combined with short-course radiotherapy (volumetric-modulated arc therapy, VMAT, 10 daily fractions of 3 Gy up to 30 Gy, days 1–5, 16–20) in the next cycle. Groups A and B both will undergo radical esophagectomy with lymphadenectomy after 4–6 weeks. After surgery, all patients will be offered voluntary immunotherapy every 3 weeks for up to 1 year, until the confirmed progressive disease or no continued clinical benefit can be obtained as per the decision of the treating physician. Participants are advised to follow up every 3 months for the first 2 years after surgery, every 6 months for the 3–5 years, and annually after 5 years.

Statistical considerations and data analysis

All endpoints will be analyzed according to the intention-to-treat principle. Continuous data will be presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] and compared between groups using the Student's *t*-test or the Wilcoxon rank sum test. Categorical variables will be described as numbers (proportion) and compared using the chi-square test or Fisher's exact test. OS and PFS are calculated the median time and cumulative incidences function using the Kaplan-Meier method and compared with the log-rank test. Longitudinal data will be conducted by a linear mixed model with treatment effect, and baseline factors influencing the endpoint as fixed effects, and the center or time as a random effect will be used to compare the PROs and QoL data. All performed tests will be two-sided with a significance level set at $P<0.05$.

Ethics and dissemination

The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. KY-Q-2022-260-03) and registered at the clinicaltrials.gov (NCT05596890). The First Affiliated Hospital of Shantou University Medical College, the First Affiliated Hospital of Guangdong Pharmaceutical University, and the General Hospital of Southern Theater Command will submit the research protocol to the ethics committees separately. All participants will be asked to sign written informed consent. The study results will be shared to the participating centers, presented at world-class conferences, and published in peer-reviewed medical journals.

Discussion

Safety considerations/patient safety

Safety assessments include monitoring and recording any ADEs and serious ADEs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and performing other protocol-specified tests. Administration of the study drugs will be performed in the presence of emergency medical facilities and staff, who have been trained in emergency monitoring and management. Laboratory examinations must be reviewed before any drug administration in every cycle. Patients will be closely monitored for clinical manifestation of autoimmune diseases and infections. Patients will be followed up for their safety for 60 days after the last administration or withdrawal from in this research. Finally, after completing or withdrawing from the study, patients who still have treatment-associated ADEs will be followed up.

Data management and quality control

Research data collection, storage, and management will be conducted in a web-based Real-World-Data Management Platform (RWDMP; https://cdo.epro-vision.com:81/html/index.html) which is stored in a password-protected cloud drive. PROs should be independently completed by participants. If participants have difficulties in completing the e-questionnaires, data collectors or their family members will help them by just reading each item and recording the participant's responses. Meanwhile, other data will also be measured, recorded, and uploaded to RWDMP.

During the whole process of clinical trials, clinical investigators should strictly follow the requirements of Good Clinical Practice. Before patients' enrolment, investigators from each research center will receive standard operation procedure training. The specific requirements are as follows: (I) researchers are responsible for obtaining informed consent signed by each subject or his/her representative; (II) the case reported forms should be filled out as uniformly required; (III) keep regular visits; and (IV) keep complete laboratory test records, clinical records and original medical records of the subjects.

Strengths and limitations of this study

This study will provide preliminary evidence for evaluating the feasibility of utilizing patient-reported dysphagia relief to assess pathological response following neoadjuvant immunochemotherapy in the early remission group (Group A) and the safety and efficacy of combining immunochemotherapy and short-course radiotherapy in the latent remission group (Group B). It will provide evidence for sparing patients who have early and persistent relief of dysphagia symptom from radiation therapy. It is the first study to apply an electronic PRO-based surveillance system in patients with ESCC treated with immunotherapy.

The study limitations include the single-arm study design and the relatively small sample size. Moreover, the specific mechanism and mediator of the effect of early dysphagia remission on the effectiveness of neoadjuvant immunochemotherapy remains to be explored in further studies.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-274/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-274/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-274/coif). G.Q. reports receiving funding from the Guangzhou Major Clinical Technology Project (No. 2023P-ZD05), the Science and Technology Program of Guangzhou, China (No. 202206010103), and the Natural Science Foundation of Guangdong Province (No. 2022A1515012469). And G.Q. reports that BeiGene provided tislelizumab for patient use in the study. The other authors have no conflicts of interest to declare.

Ethical Statement: 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. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study has been approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. KY-Q-2022-260-03) and registered at the clinicaltrials.gov (NCT05596890). The First Affiliated Hospital of Shantou University Medical College, the First Affiliated Hospital of Guangdong Pharmaceutical University, and the General Hospital of Southern Theater Command will submit the research protocol to the ethics committees separately. All participants will be asked to sign written informed consent. The study results will be shared to the participating centers, presented at world-class conferences, and published in peer-reviewed medical journals.

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