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Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A randomized controlled trial protocol

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Abstract

Introduction: Radiation-induced lung injury (RILI) is among the most clinically-challenging toxicities and dose-limiting factors during/after thoracic radiation therapy for esophageal squamous cell carcinoma (ESCC). With limited effective protective drugs against RILI, the main strategy to reduce its likelihood is strict adherence to dose-volume constraints of normal lung. RILI can manifest as acute radiation pneumonitis of cellular injury, cytokine release, and cytokine recruitment of inflammatory infiltrate, and the ensuing chronic radiation pulmonary fibrosis. Pirfenidone inhibits inflammatory cytokines, scavenges free radicals, and reduces hydroxyproline and collagen formation. Hence, pirfenidone appears to be promising for RILI prevention. This study aims to evaluate the efficacy and safety of pirfenidone in preventing RILI in patients with locally advanced ESCC receiving chemoradiotherapy.

Methods and analysis: This study has been designed as a randomized, placebo-controlled, double-blind, single-center phase 2 trial and will explore whether the addition of pirfenidone during concurrent chemoradiation therapy (CCRT) will prevent RILI in patients with locally advanced ESCC unsuitable for surgery. Eligible participants will be randomized 1:1 to pirfenidone or placebo. The primary endpoint is the incidence of grade ≥2 RILI. The secondary endpoints include the incidence of any grade RILI, the time to the occurrence of RILI, the changes in pulmonary function after CCRT, the completion rate of CCRT, disease-free survival (DFS), and overall survival (OS). The follow-up will be 1 year. If the results meet the primary endpoint of this trial, a phase 3 multicenter trial with larger sample size will be needed to conclusively demonstrate the benefits of pirfenidone for preventing RILI.

Ethics and dissemination

Ethics approval has been obtained from the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). The findings of the trial will be disseminated through peer-reviewed journals, national and international conference presentations.

Trial registration number: ChiCTR2100043032; Pre-results

Strengths and limitations of this study

- This is the first randomized controlled trial to explore the efficacy and safety of pirfenidone in preventing RILI.
- It is a double-blind trial that neither patients nor physicians will be masked to treatment allocation.
- It is a phase 2 trial performed at a single center.
- The dosage of radiation was inconsistent, with unresectable patients receiving 50 Gy to 60 Gy, and with downstaging patients receiving 40 Gy due to further conversion to surgical resection.

Key words: pirfenidone; radiation-induced lung injury; prevention; esophageal squamous cell carcinoma; concurrent chemoradiation therapy; randomized controlled trial.

Introduction

Esophageal cancer ranks the eighth most common cause of cancer in the world. Among the 477,900 new patients reported globally per year, nearly a half occur in China, and 90% of them are esophageal squamous cell carcinoma (ESCC).[1] The standard of care for unresectable locally advanced ESCC remains definitive concurrent chemoradiation therapy, with a 3-year OS rate of 30%-37%.[2-5] Because the lungs often lay in the path of the treatment beams, radiation-induced lung injury (RILI) is one of the most common complications and potentially dose-limiting toxicities of radiotherapy for esophageal cancer, with an incidence of about 10.7%-35.14%.[6-11] Furthermore, RILI during radiation can delay or even interrupt radiotherapy, resulting in poor local disease control, increased financial burden, and even death.

Although advanced radiotherapy technologies such as intensity-modulated radiation therapy (IMRT) are superior to traditional 2D and 3D conformal radiation therapy regarding dosimetry and organ protection,[10 12] many patients still develop varying degrees of RILI.[13] In clinical practice, there is no specific treatment for RILI except oxygen inhalation, glucocorticoids administration, and application of antibiotics when necessary. Therefore, preventing RILI is of greater clinical significance than treating it. Although amifostine has been approved by the US Food & Drug Administration (FDA) for radiotherapy protection, it did not show significant efficacy in protecting against RILI during treatments for esophageal cancer.[14 15] Moreover, its clinical application is limited owing to the high price and high rates of side effects. Therefore, there are few effective protective strategies against RILI during radiation therapy for patients with ESCC.

Pirfenidone is an active small-molecule oral drug that can inhibit the

overexpression of transforming growth factor (TGF)-β1 and meanwhile reduce the secretion of platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), thereby inhibiting the biological activity of fibroblasts.[16-18] Pharmacodynamic experiments showed that pirfenidone had satisfying effects against lung inflammation and fibrosis.[19-22] The FDA approved pirfenidone in 2014 to treat idiopathic pulmonary fibrosis (IPF),[23 24] which shares some common pathological processes with RILI.[25 26] A study in mice showed that pirfenidone could attenuate RILI.[27] A phase 2 trial is under recruitment and aims to confirm the efficacy of pirfenidone for the treatment of RILI (ClinicalTrials.gov NCT03902509) rather than for its prevention.

There are no published clinical data to assess the preventive role of pirfenidone against RILI. Therefore, this randomized, placebo-controlled, double-blind, single-center, phase 2 trial was designed to examine whether pirfenidone can reduce the incidence of RILI in patients with locally advanced ESCC receiving CCRT.

Methods

Study design and participants

This study is a randomized, placebo-controlled, double-blind, single-center, phase 2 clinical trial to examine the preventive role of pirfenidone for RILI in patients with unresectable locally advanced ESCC undergoing CCRT. The participants will be randomized 1:1 to the pirfenidone or control groups. Figure 1 presents the overview of the study flowchart.

The full inclusion, exclusion, and withdrawal criteria are listed in Table 1.

All eligible patients must sign a written informed consent and be willing to participate in and complete the study and follow-up.

Pre-treatment assessment and screening

Each patient must complete the following examinations and counseling within 1 or 2 weeks before entering the trial:

1) Detailed medical history review.

2) Physical examination (height, weight, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status).

3) Blood tests, including complete blood counts (CBC), biochemical profiles, coagulation function, hepatitis B virus (HBV) screening and HBV DNA (for HBsAg-positive patients), esophageal cancer-related tumor markers of carcinoembryonic antigen (CEA), cancer antigen (CA) 199, CA125, CA153, neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCC), soluble fragment of cytokeratin 19 (Cyfra21-1), and α-fetoprotein (AFP).

4) Cardiopulmonary function, including electrocardiogram, ultrasonic cardiogram, and pulmonary function.

5) Upper gastrointestinal endoscopy and biopsy.

6) Imaging, including chest/abdominal computed tomography (CT) with intravenous contrast, upper gastrointestinal swallowed meglumine diatrizoate contrast, pelvic CT with contrast as clinically indicated, and FDG-PET/CT evaluation if the patient agrees, leading to more accurate staging.

7) Nutritional assessment and counseling.

8) Smoking cessation advice.

Radiotherapy

The target contour principle is as follows. Gross tumor volume (GTV) should include the primary tumor (GTVp) and enlarged regional lymph nodes (GTVn) by the planning scan and other diagnostic imaging examinations. Elective node irradiation (ENI) is used for clinical target volume (CTV) delineation. CTV of GTVp is defined

as the primary tumor plus a 3-cm expansion superiorly and inferiorly along the length of the esophagus and a 0.5-1-cm radial expansion including the para-esophageal lymph nodes. CTV of GTVn should cover all involved and high-risk lymphatic drainage regions such as the supraclavicular for the super-thoracic and middle-thoracic sections.[28] Planning target volume (PTV) for GTV and CTV shall be created by expanding with a uniform margin of 0.5 cm separately.

Bilateral lungs, heart, spinal cord, stomach, and liver are identified as organs at risk (OAR) and should be limited as follows: 1) lungs: ≤28%-30% of irradiated bilateral lung volume exceeding 20 Gy (V20), V5 ≤60%, and mean lung dose (MLD) <15 Gy; 2) heart: V40 <30%, V40 ≤30%, and mean dose≤30 Gy; 3) spinal cord: maximal dose (Dmax) ≤45 Gy; 4) stomach: V40 ≤40% and Dmax ≤55-60 Gy; and 5) liver: V30 ≤40% and mean dose <25 Gy.

The prescribed dose to PTV-CTV and PTV-GTV are 50.4 Gy/1.8 Gy/28 fractions and 60 Gy/1.8 Gy/33 fractions, respectively. If the target area is large and OAR cannot be achieved, only PTV-GTV irradiation or PTV-CTV irradiation can be performed as decided by the treating radiotherapist. The prescription dose has to cover at least 95% of the PTV. Either volumetric-modulated arc therapy (VMAT) or IMRT is recommended for irradiation. Resectability will be re-assessed by a multidisciplinary tumor board at irradiation to 41.4 Gy for patients unsuitable for surgery at diagnosis. If possible for surgical resection, then radiation therapy will be terminated and the operation will perform after 4-8 weeks after termination of radiation.

Chemotherapy

The participants receive docetaxel 60 mg/m^2 intravenously on day 1 and cisplatin 30 mg/m^2 intravenously on days 1 and 2 (DP regimen) for two cycles. Polyethylene

glycol recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is recommended for prevention of neutropenia during CCRT. Dose modification should be based on the preceding cycle CBC and biochemical markers. The chemotherapy can be continued if 1) absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L, 2) platelet count $\geq 100\times10^9$/L, 3) alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin are CTC grade <2, and 4) non-hematological toxicity (except for hair loss) returns to grade 1 or baseline level. The doses of both drugs should be decreased by 20% if any grade 3 or higher toxicities are observed. If grade 3 or 4 radiation pneumonitis occurs, radiotherapy and concurrent chemotherapy are terminated.

Randomization and intervention

The participants will be randomized 1:1 to the pirfenidone or control groups using a random number table and stratified according to the reasons whether they cannot tolerate surgery or the tumor cannot be removed surgically. Both the participants and the doctors are masked from grouping. Both pirfenidone and placebo capsules are provided by Beijing Continent Pharmaceutical Co., Ltd. The appearance, smell, taste, and properties of the placebo are the same as the study drug. Each capsule contains 100 mg of drug/placebo. In the first week, the dosage is 200 mg/time, 3 times/day. In the second week, the dosage is increased to 300 mg/time, 3 times/day. In weeks 3-12, the dosage is increased to 400 mg/time, 3 times/day. The pirfenidone treatment starts on the day when radiotherapy starts and lasts for 12 weeks. The capsules are taken during or after meals as gastrointestinal reactions are the most common adverse effects of pirfenidone. Photosensitivity is another common adverse event. External use of sunscreen and avoiding the sun during medication can effectively reduce the incidence and severity of photosensitivity. If the adverse events still occur or cannot be tolerated even after the dose is reduced, the drug can be

temporarily discontinued for 1-2 weeks until the participant tolerates the symptoms. Once the adverse events recover or can be tolerated, the participant can retake pirfenidone. The physician can decide whether to stop the drug according to the situation. The pirfenidone treatment should be permanently discontinued if severe adverse events occur, including liver dysfunction, jaundice, severe hypersensitivity, and photosensitivity.

Concomitant medication

Drugs that may prevent or treat fibrosis are forbidden, such as amifostine and thalidomide. The participants should avoid the concurrent use of drugs that increase the adverse reactions of pirfenidone, including ciprofloxacin, amiodarone, and propafenone. The participants should also avoid the concurrently receive of that can reduce the efficacy of pirfenidone, such as omeprazole and rifampin.

Endpoints

The primary endpoint is the incidence of grade 2 or higher RILI in participants in the full analysis set (FAS) and per-protocol set (PPS). RILI will be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 within 1 year. The secondary endpoints include the incidence of RILI of any grade, the time to the occurrence of RILI, changes in pulmonary function after radiotherapy, the completion rate of CCRT, disease-free survival (DFS), and overall survival (OS).

Follow-up

1. During intervention

1) CBC and biochemical profiles will be checked once a week during the treatment period.

2) Physical examination and nutritional score assessment are performed once a week.

3) Pulmonary function and CT are performed after 23 fractions to assess tumor regression and surgery opportunities.

2. Post-treatment

The follow-up period is 1 year or until the participant's death. All participants are followed at 1 month after radiotherapy and every 3 months thereafter or as needed clinically. Routine follow-up should include clinical symptoms, CBC, tumor markers, contrast-enhanced CT, upper gastrointestinal contrast, pulmonary function. Gastroscopy is recommended to be reviewed for the first year. If there is a suspicion of recurrence, another gastroscopy can be performed. If necessary, PET-CT imaging and brain MR can be performed.

Statistical analysis

According to the retrospective study in the authors' hospital and literature review, [7 8 29-31] it is assumed that the occurrence rate of RILI grade ≥2 in the control group will be 25% and that in the pirfenidone group will be 10%. This trial is designed as a randomized phase 2 study with a two-sided α of 0.20 and a power of 80%,[32] using PASS version 15.0.5 to calculate the sample size. In a phase 2 screening design, a higher α level than the 0.05 level is used for the next phase 3 design. If the phase 2 trial is positive, such a positive result is not usually considered definitive without a subsequent phase 3 trial. In this study, 36 participants should be included in each group with α of 0.2 and power of 80%. Considering a dropout rate of 20%, it is planned to enroll about 88 participants.

All analyses will be performed using SAS Version 9.3 (SAS Institute, Cary, NC, USA). The t-test will be used for continuous data. The chi-square test and Fisher's exact probability method will be used for categorical data. The survival rate will be calculated using the Kaplan-Meier method, and comparisons between groups will be

performed using the log-rank test. The confidence interval of the survival distribution will be calculated according to Greenwood's formula. A proportional hazard regression model for risk will be estimated using hazard ratios. $P<0.05$ will be considered statistically significant.

Data collection and management

All clinical data will be collected by a research assistant and recorded in detail in the predesigned electronic table. All written informed consent will be stored in a separate closet, and only the main researchers can access the relevant research data. All study procedures were developed to ensure data protection and confidentiality.

Dissemination

The results will be disseminated in international peer-reviewed conferences and journals.

Patient and public involvement

The patients and the public were not involved in the development of this protocol.

Discussion

RILI is an important dose-limiting factor in thorax cancer radiotherapy. It is commonly categorized into the acute injury stage, radiation pneumonitis (RP), and the subsequent chronic injury stage, i.e., radiation pulmonary fibrosis (RPF). Immediately after radiation exposure, damage to type I and II alveolar epithelial cells leads to vascular permeability, cytokine release, and inflammatory cell infiltration, causing acute pneumonitis. Then, injury repair in the late phase results in pulmonary fibrosis [33].

The only FDA-approved cytoprotective agent is amifostine, but its limited effectiveness and adverse reactions prevent its clinical application.[14 15 34 35]

Consequently, there is a great focus on agents that are clinically applicable, especially for the prevention of RILI.

Pirfenidone is a small molecule biosynthetic drug with anti-inflammatory, anti-fibrosis, and antioxidant effects.[16-18 36] The FDA approved it for the management of IPF.[23 24 37-39] As RILI has similar pathological processes and clinical manifestations as IPF, characterized by cell infiltration, interstitial edema, and interstitial fibrosis of the alveolar wall,[26] pirfenidone is promising in the prevention and treatment of RILI. Ji et al. [40] found that pirfenidone could significantly reduce inflammation and collagen deposition through decreasing macrophages and hydroxyproline levels in alveolar macrophages and lung tissues of irradiated rats by 62% and 24%, respectively. Another in vitro experiment by Qin et al. [27] showed that pirfenidone prevented RILI by suppressing the expression of TGF-β1 and phosphorylation of Smad3 in lung tissues and significantly prolong the survival of rats after irradiation (>140 days vs. 73 days, $P<0.01$). Sun et al. [41] also confirmed the prevention from pelvic fibrosis caused by radiotherapy for rectal cancer.

As early as 2007, an open-label, prospective pilot study [42] was carried out to ameliorate established radiation-induced fibrosis of the neck, back, or extremities that caused at least a moderately severe loss of range of motion. The results reported an improvement of the function of at least 25% and subjective improvement.

Currently, a national multicenter study on the treatment of RILI with pirfenidone led by Prof. Wang and Prof. Chen is ongoing (NCT03902509). Still, no clinical study on the prevention of RILI with pirfenidone has been reported. According to its mechanism, pirfenidone is supposed to be promising in preventing RILI. Since the target volume, target location, and radiotherapy dose for esophageal cancer and lung cancer are different, this preliminary study was designed to explore the efficacy of

pirfenidone in preventing RILI, focusing on patients with middle and upper ESCC.

The present randomized, placebo-controlled, double-blind, single-center phase 2 trial is designed to determine the efficacy and safety of pirfenidone in preventing RILI in participants with locally advanced ESCC undergoing CCRT. The results might provide new options for the prevention of RILI. Further research is needed to confirm the efficacy of pirfenidone for the prevention of RILI in a multicenter phase 3 trial with larger sample size.

List of abbreviations

AE: adverse event; AFP: α-fetoprotein; ALT: alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; CA: cancer antigen; CCr: creatinine clearance rate; CEA: carcinoembryonic antigen; CT: computed tomography; CTV: clinical target volume; Cyfra21-1: soluble fragment of cytokeratin 1; DFS: disease-free survival; Dmax: maximal dose; ECOG: Eastern Cooperative Oncology Group; FGF: fibroblast growth factor; GTV: gross tumor volume; IL: interleukin; IPF: idiopathic pulmonary fibrosis; MD: mean dose; NRS: nutritional risk scale; NSE: neuron-specific enolase; OS: overall survival; PDGF: platelet-derived growth factor; PET: positron emission tomography; PTV: planned target volume; RILI: radiation-induced lung injury; SCC: squamous cell carcinoma antigen; SCr: serum creatinine; TGF: tumor growth factor; TNF: tumor necrosis factor; ULN: upper limit of normal; WBC: white blood cells.

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Authors' contributions

XBH is the principal investigator responsible for study design, revised the article critically, and approved the final version to be published. Chen Cheng mainly participated in protocol design and writing. ZBW and YY is responsible for statistical and study design. Chen Chun and KMQ are responsible for surgery indication. XD, CRX, LSQ and ZHL made a substantial contribution to the design of the study. All authors read and approved the final manuscript.

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Competing interest statement

All authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). Signed informed consent from each participant is required. The trial has been registered in chictr.org.cn (ChiCTR2100043032).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Not applicable – data collection is still ongoing.

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Figure legend

Figure 1. Study flowchart.

Table 1. Full inclusion, exclusion and withdrawl criteria.

Inclusion criteria	Exclusion criteria	Withdrawal criteria
● Age between 18 and 75 years old. ● ECOG performance status of 0-1. ● Pathological confirmation of ESCC. ● Imaging staging suggests $T_{3-4}N+M0$ thoracic esophageal cancer according to AJCC 8 staging (primary lesions are mainly in the chest cavity). ● No restriction on the number of regional nodal stations or bulk of disease. ● Patients who cannot tolerate surgery or the tumor cannot be removed surgically. ● No perforation or deep niche in the esophageal cancer lesion. ● No prior chemotherapy, immunotherapy, or surgery	● History of chest radiotherapy. ● Concomitant tumor in other organs or prior malignancies within 5 years. ● History of interstitial lung disease or non-infectious pneumonia. ● Severe cardiovascular disease, cerebrovascular complications, epilepsy, active peptic ulcers, infections, psychological disorders, or other serious underlying diseases that may limit their understanding and tolerance of comprehensive treatments.	● Treatment delay for more than 2 weeks or interruption due to extended toxicity. ● Disease progression is judged by researchers during treatment.

before radiotherapy. ● Able to eat liquid food. ● Adequate bone marrow, liver, kidney, blood coagulation function, and lung functions. ● Life expectancy of >6 months. ● Voluntary participation in the study, with good expected compliance.	● Patients with a previous history of ataxia due to telangiectasia or other radiosensitivity reaction. ● Patients with scleroderma or active connective tissue disease.

ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; AJCC, American Joint Committee on Cancer; CT, computed tomography.

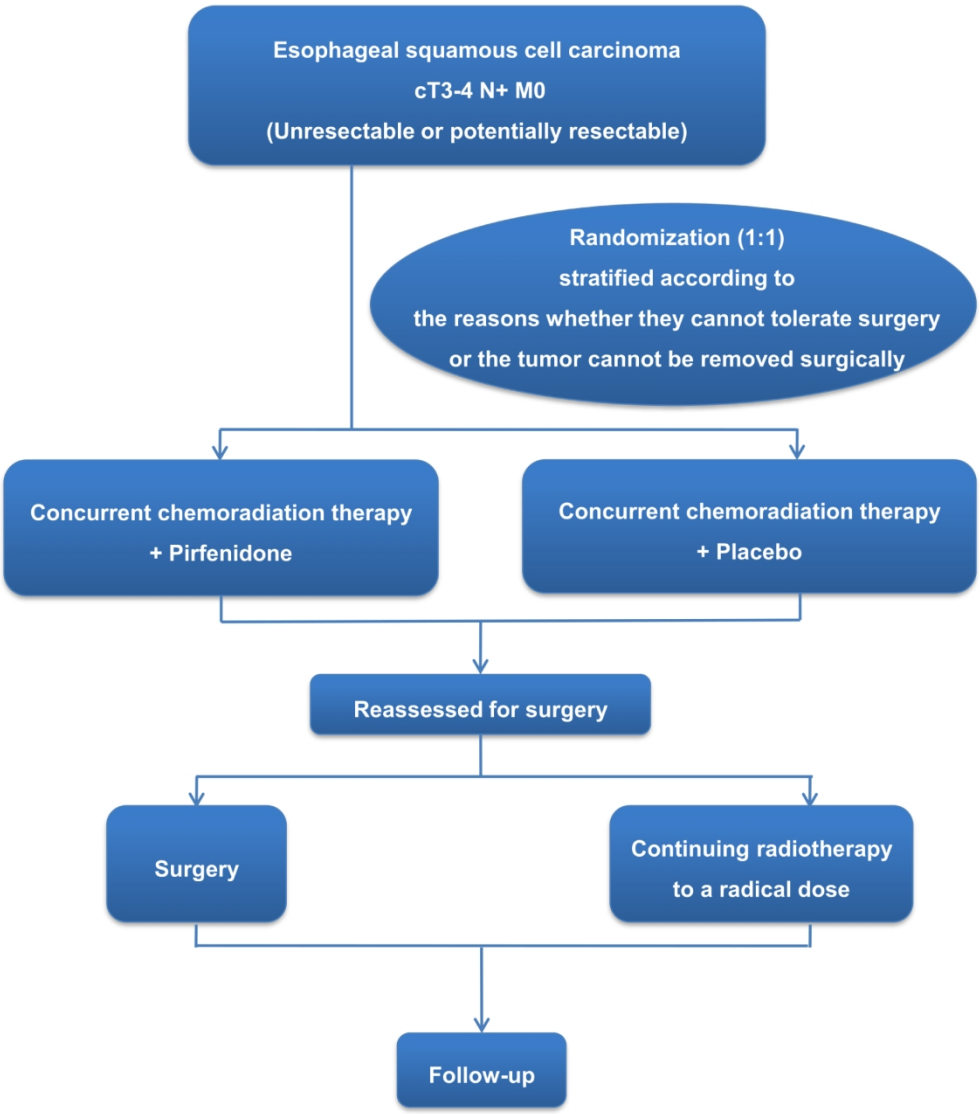

Figure 1. Study flowchart.

170x194mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,13
	5b	Name and contact information for the trial sponsor	/
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-9,Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	/
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	/
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	/
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6,9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	/
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	/
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	/
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	/
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A randomized controlled trial

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	IMAGING, Adult radiotherapy < RADIOTHERAPY, Radiation oncology < RADIOTHERAPY

Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A randomized controlled trial

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Abstract

Introduction: Radiation-induced lung injury (RILI) is among the most clinically-challenging toxicities and dose-limiting factors during and/or after thoracic radiation therapy for esophageal squamous cell carcinoma (ESCC). With limited effective protective drugs against RILI, the main strategy to reduce the injury is strict adherence to dose-volume restrictions of normal lungs. RILI can manifest as acute radiation pneumonitis of cellular injury, cytokine release, and cytokine recruitment to inflammatory infiltrate, and subsequent chronic radiation pulmonary fibrosis. Pirfenidone inhibits inflammatory cytokines, scavenges free radicals, and reduces hydroxyproline and collagen formation. Hence, pirfenidone might be a promising drug for RILI prevention. This study aimed to evaluate the efficacy and safety of pirfenidone in preventing RILI in patients with locally advanced ESCC receiving chemoradiotherapy.

Methods and analysis: This study is designed as a randomized, placebo-controlled, double-blinded, single-center phase 2 trial and will explore whether the addition of pirfenidone during concurrent chemoradiation therapy (CCRT) will prevent RILI in patients with locally advanced ESCC unsuitable for surgery. Eligible participants will be randomized at 1:1 to pirfenidone or placebo group. The primary endpoint is the incidence of grade ≥2 RILI. The secondary endpoints include the incidence of any grade other than grade >2 RILI, the time to the occurrence of RILI, the changes in pulmonary function after CCRT, the completion rate of CCRT, disease-free survival (DFS), and overall survival (OS). The follow-up period will be 1 year. If the results meet the primary endpoint of this trial, a phase 3 multicenter trial with a larger sample size will be required to substantiate the evidence of benefits of pirfenidone for preventing RILI.

Ethics and dissemination

This study was approved by the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). The findings of the trial will be disseminated through peer-reviewed journals, and national and international conference presentations.

Trial registration: ChiCTR2100043032

Strengths and limitations of this study

- This is the first randomized controlled trial to explore the efficacy and safety of pirfenidone in preventing RILI.
- It is a double-blinded trial that neither patients nor physicians will know the treatment allocation.
- It is a phase 2 trial performed at a single center.
- The dosage of radiation was inconsistent, with patients with unresectable patients receiving 50 Gy to 60 Gy, and with patients in the process of downstaging receiving 40 Gy due to further option to surgical resection.

Key words: Pirfenidone; radiation-induced lung injury; prevention; esophageal squamous cell carcinoma; concurrent chemoradiation therapy; randomized controlled trial.

Introduction

Esophageal cancer ranks the eighth most common cancer worldwide. Among the 477,900 new patients reported globally per year, nearly a half number of the cases occur in China, and 90% of them are ESCC.[1] The definitive standard of care for unresectable locally advanced ESCC remains concurrent chemoradiation therapy, with a 3-year OS rate of 30%-37%.[2-5] Because the lungs often lay in the path of the treatment radiation beams, RILI is inevitable. It is one of the most common side effects and potentially dose-limiting toxicities of radiotherapy for esophageal cancer, with an incidence of about 10.7%-35.14%.[6-11] Furthermore, RILI during radiation can delay or even interrupt radiotherapy, resulting in poor local control of the disease, increased financial burden, and even death.

Although advanced radiotherapy technologies such as intensity-modulated radiation therapy (IMRT) are superior to traditional 2D and 3D conformal radiation therapies regarding dosimetry and organ protection,[10 12] many patients still develop varying degrees of RILI.[13] In clinical practice, there is no specific treatment for RILI except oxygen inhalation, glucocorticoid administration, and application of antibiotics when necessary. Therefore, preventing RILI is of greater clinical significance than treating it. Although amifostine was approved by the US Food & Drug Administration (FDA) for radiotherapy protection, it did not efficiently protect against RILI during the course of treatments for esophageal cancer.[14 15] Moreover, its clinical application is limited owing to the high price and high rates of its side effects. Therefore, there are a few effective protective strategies against RILI during radiation therapy for patients with ESCC.

Pirfenidone is an active small-molecular oral drug that can inhibit the

overexpression of transforming growth factor (TGF)-β1 and meanwhile reduce the secretion of platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF), thereby inhibiting the biological activity of fibroblasts.[16-18] Pharmacodynamic experiments showed that pirfenidone had satisfying effects against lung inflammation and fibrosis.[19-22] The FDA approved pirfenidone in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF),[23 24] which shares some common pathological manifestations with RILI.[25 26] A previous study in mice showed that pirfenidone could attenuate RILI.[27] A phase 2 trial is under recruitment stage and aims to confirm the efficacy of pirfenidone for the treatment of RILI (ClinicalTrials.gov NCT03902509).

There are no published clinical data to assess the prophylactic preventive role of pirfenidone against RILI. Therefore, this randomized, placebo-controlled, double-blinded, single-center, phase 2 trial is designed to examine whether pirfenidone can reduce the occurrence of RILI in patients with locally advanced ESCC receiving CCRT.

Methods

Study design and participants

This study is a randomized, placebo-controlled, double-blinded, single-center, phase 2 clinical trial to examine the preventative role of pirfenidone for RILI in patients with unresectable locally advanced ESCC at diagnosis undergoing CCRT. The participants will be randomized at 1:1 to the pirfenidone or control groups. Figure 1 depicts the overview of the study procedure.

The full inclusion, exclusion, and withdrawal criteria are listed in Table 1.

All eligible patients should provide a written informed consent and be willing to

participate in and complete the study and follow-up.

Pre-treatment assessment and screening

Each patient must complete the following examinations and undergo counseling within 1 or 2 weeks before the onset of the trial:

1) Detailed medical history review.

2) Physical examination (height, weight, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status).

3) Blood tests, including complete blood counts (CBC), biochemical profiles, coagulation function, hepatitis B virus (HBV) screening and HBV DNA (for HBsAg-positive patients), esophageal cancer-related tumor markers such as carcinoembryonic antigen (CEA), cancer antigen (CA) 199, CA125, CA153, neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCC), soluble fragment of cytokeratin 19 (Cyfra21-1), and α-fetoprotein (AFP).

4) Cardiopulmonary function evaluation, including electrocardiogram, ultrasonic cardiogram, and pulmonary function assessment.

5) Upper gastrointestinal endoscopy and biopsy.

6) Imaging, including chest/abdominal computed tomography (CT) with intravenous contrast and upper gastrointestinal swallowed meglumine diatrizoate contrast, pelvic CT with contrast as clinically indicated, and [18F] fluorodeoxyglucose positron emission tomography/computed tomography ([18F] FDG-PET/CT) evaluation if the patient agreed to undergo, leading to more accurate staging.

7) Nutritional assessment and counseling.

8) Smoking cessation advice.

Radiotherapy

The target contour principle is as follows. Gross tumor volume (GTV) include the primary tumor (GTVp) and enlarged regional lymph nodes (GTVn), and are determined by the CT simulation scan and other diagnostic imagings. Elective node irradiation (ENI) will be used for clinical target volume (CTV) delineation. CTV of GTVp is defined as the primary tumor volume plus a 3cm margin expansion in superior and inferior along the length of the esophagus and a 0.5-1cm radial expansion including the para-esophageal lymph nodes. CTV of GTVn will cover all lymph nodes involved and high-risk lymphatic drainage regions such as the supraclavicular for the super-thoracic and middle-thoracic sections.[28] Planning target volume (PTV) for GTV and CTV will be created by expanding with a uniform margin of 0.5 cm separately. The recommended dose to PTV-CTV and PTV-GTV are 50.4 Gy/1.8 Gy/28 fractions and 60 Gy/1.8 Gy/33 fractions, respectively. If the target area is large and OAR can't be achieved, only PTV-GTV irradiation or PTV-CTV irradiation can be performed as decided by the treating radiotherapist. The administering dose will cover at least 95% of the PTV. Normal tissue tolerance dose-limits are listed in Table 2. All patients will be positioned supine on the treatment couch and fixed by a custom-fitted thermoplastic sheet and the setup imaging will be acquired every day before treatment to correct the treatment position by OBI image system. IMRT is recommended when the treatment plans were designed. Because the dose calculation for areas with artifacts generates heterogeneity, leading to

high dose deviation. To ensure the quality of radiotherapy delivered, the Acuros XB (version 15.5) dose algorithm which was reported to be as accurate as or close to the Monte Carlo simulation (MC) method will be employed in this present study. The treatment plan for all patients will be verified using phantom named Delta4, and the gamma passing rate at the criteria of 3%/3 mm will be ensured greater than 98%.

Resectability will be re-assessed by a multidisciplinary team at irradiation with 41.4 Gy. If surgical resection is possible, radiation therapy will be terminated, and the surgery will be performed after 4-8 weeks after termination of radiation.

Chemotherapy

The participants will receive docetaxel at 60 mg/m^2 intravenously on day 1 and cisplatin at 30 mg/m^2 intravenously on days 1 and 2 (DP regimen) for two cycles. Polyethylene glycol recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is recommended for prevention of neutropenia during CCRT. Dose modification will be based on the preceding cycle CBC and biochemical markers. The chemotherapy will be continued if 1) absolute neutrophil count (ANC) is $\geq 1.5\times10^9$/L, 2) platelet count is $\geq 100\times10^9$/L, 3) alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin are of Common Terminology Criteria for Adverse Events (CTCAE) grade <2, and 4) non-hematological toxicity (except for hair loss) returns to grade 1 or baseline level. The doses of both drugs will be decreased by 20% if any grade 3 or higher toxicities are observed. If grade 3 or 4 radiation pneumonitis occurs, radiotherapy and concurrent chemotherapy will be terminated.

Randomization and intervention

The participants will be randomized at 1:1 to the pirfenidone or control groups using a random number table and stratified based on the tolerability or inability to surgery. Participants and doctors will be masked to treatment allocation. Identical pirfenidone and placebo capsules are provided by Beijing Continent Pharmaceutical Co., Ltd. The appearance, smell, taste, and properties of the placebo are the same as the study drug. Each capsule contains 100 mg of drug or placebo. In the first week, the dosage will be 200 mg/time, 3 times/day. In the second week, the dosage will be increased to 300 mg/time, 3 times/day. In weeks 3-12, the dosage will be increased to 400 mg/time, 3 times/day. The pirfenidone treatment will start on the day when radiotherapy will be initiated and lasted for 12 weeks.The capsules will be taken during or after meals as gastrointestinal reactions are the most common adverse effects of pirfenidone. Photosensitivity is another common adverse event. External use of sunscreen and avoiding the sun during medication can effectively reduce the incidence and severity of photosensitivity reactions. If the adverse events still occur or cannot be tolerated even after the dose is reduced, the drug will be temporarily discontinued for 1-2 weeks until the participant tolerates the symptoms. Once the adverse events are alleviated or can be tolerated, the participant will retake pirfenidone. The physician can decide whether to stop the drug intake according to the situation. The pirfenidone treatment will be permanently discontinued if severe adverse events occur, including liver dysfunction, jaundice, severe hypersensitivity, and photosensitivity.

Concomitant medication

Drugs that may prevent or treat fibrosis are forbidden, such as amifostine and thalidomide. The participants should avoid the concurrent use of drugs that increase the adverse reactions of pirfenidone, including ciprofloxacin, amiodarone, and

propafenone. The participants should also avoid the concurrently receipt of medications that can reduce the efficacy of pirfenidone, such as omeprazole and rifampin.

Endpoints

The primary endpoint is the incidence of grade 2 or higher RILI in participants of the full analysis set (FAS) and per-protocol set (PPS). RILI will be evaluated according to CTCAE version 5.0.[29] within 1 year. The secondary endpoints include the incidence of RILI of any grade, the time to the occurrence of RILI, and changes in pulmonary function after radiotherapy, the completion rate of CCRT, disease-free survival (DFS), and overall survival (OS).

RLIL is a diagnosis established by clinical suspicion or radiological findings after excluding other lung pathologies such as pre-existing pathologies and pulmonary infection. It often appears with no specific symptom, vital signs, laboratory profiling or imaging tests. Familiar history of radiation and recognition of RILI are of utmost importance in the context of regular follow-up. Diagnosis and grading will be confirmed by review by multidisciplinary senior physicians, including a radiation oncologist, a pulmonologist, and a radiologist. History, physical, chest CT, and previous radiotherapy will be evaluated at every follow-up during personal visits when available. RILI will be scored based on the CTCAE version 5.0 classifying symptoms and image findings will be used to classify into five grades[29] As far as the symptom, dyspnea and dry cough are the most common manifestation–in acute lung injury. [30] Occasional fever is usually mild, but high fever is sometimes reflective of co-infectious pneumonitis. The chronic RF is a slowly progressing respiratory disease that can

manifest as respiratory insufficiency. In terms of physical symptoms, the physical examination findings may be normal or include pleural rub, moist rales, and signs of consolidation. Chest imaging, particular lung CT at baseline and follow-up are critical in the diagnosis and grading. In acute phase, which usually appears 4-8 weeks after radiotherapy, CT images may display exudative changes such as multiple small patchy or flock-shaped ground glass density shadows in the irradiation field, with fuzzy edge and unclear boundary with surrounding lung tissue. In phase of consolidation, which usually occurs 2-3 months after radiotherapy, CT images may display patchy high-density consolidation in the irradiation field, not distributed according to the lung lobe and lung segment, accompanied by partial air bronchial signs. In the stage of fibrosis, which usually occurs six months after radiotherapy, CT images may show density enhancement shadows of grid, cord, and patchy shape in the irradiation field with clear boundaries, accompanied by thickened pleura, lung volume reduction, lung hilum reduction, ipsilateral vascular texture thinning, and compensatory increase in contralateral lung volume.[31-35]

Considering the anti-inflammatory and anti-fibrotic properties of pirfenidone, the grade will be scored at the maximal level in the case who experiences with RP and RF. When one case shows grade 3 RP and grade 2 RF, it will be recorded as grade 3 for the primary endpoint.

Follow-up

1. During the period of intervention

1) CBC and biochemical profiles will be verified once a week.

2) Physical examination and nutritional score assessment will be performed once a week.

3) Pulmonary function and chest/abdominal CT will be performed after 23 fractions to assess tumor regression and surgery opportunities.

2. Post-treatment

The follow-up period is 1 year or until the participant's death. All participants will be followed at 1 month after radiotherapy and every 3 months thereafter or as needed clinically. Routine follow-up will include assessment of clinical symptoms, CBC and tumor markers, performing contrast-enhanced CT and upper gastrointestinal contrast, and pulmonary function evaluation. Repeated gastroscopy is recommended for the first year. If recurrence has is suspected, physical examination, radiography, and pathological examination will be performed.

Statistical analysis

Based on the retrospective study in the authors' hospital and literature reviews, [7 8 36-38] it is assumed that the occurrence rate of RILI of grade ≥2 in the control group will be 25% and that in the pirfenidone group will be 10%. This trial is designed as a randomized phase 2 study with a two-sided α of 0.20 and a power of 80%,[39] using PASS software version 15.0.5 to calculate the sample size. From a phase 2 screening design, a higher α level than the 0.05 level will be used for the next phase 3 design. If the phase 2 trial is positive, such a positive result is not usually considered definitive without a subsequent phase 3 trial. In this study, 36 participants will be included in each group

with α-level of 0.2 and power of 80%. Considering a dropout rate of 20%, it is planned to enroll about 88 participants.

All analyses will be performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). The t-test will be used for analyzing continuous data. The chi-square test and Fisher's exact probability method will be used for analyzing categorical data. The survival rate will be calculated using the Kaplan-Meier method, and comparisons between groups will be performed using the log-rank test. The confidence interval of the survival distribution will be calculated according to Greenwood's formula. A proportional hazard regression model for risk will be estimated using hazard ratios. $P<0.05$ will be considered statistically significant.

Data collection and management

All clinical data will be collected by a research assistant and recorded in detail in the predesigned electronic table. All written informed consent will be stored in a separate closet, and only the researchers can access the relevant research data. All study procedures were developed to ensure data protection and confidentiality.

Dissemination

The results will be disseminated in international peer-reviewed conferences and journals.

Patient and public involvement

Patients and the public are not involved in the design or conduct of the study or the outcome measures.

Discussion

For many years, radiotherapy (RT) has been employed for the treatment of esophageal cancer as curative or palliative. However, RILI is a common and severe side effect of radiation, which can delay or interrupt antitumor therapy, resulting in poor local control of the disease, impaired quality of life, and even death. Therefore, prophylactic drugs to minimize the toxicity and maximize efficacy of RT are required. Until now the only FDA-approved cytoprotective agent is amifostine, but its limited effectiveness and significant side-effect prevent its clinical application.[14, 15, 34, 35] Consequently, pharmaceutical agents that are clinically applicable, especially for the prevention of RILI are being focused[40-42]Pirfenidone is a small molecular biosynthetic drug with anti-inflammatory, anti-fibrotic, and antioxidant properties,[16-18 43] which was approved by the FDA for the management of IPF.[23 24 44-46] As RILI has similar pathogenesis and clinical manifestations as IPF, characterized by cell infiltration, interstitial edema, and interstitial fibrosis of the alveolar wall,[26] pirfenidone may hold promise for prevention and treatment of RILI, which has been tested in preclinical and pilot studies.[47, 27, 48, 49] Currently, a multicenter phase Ⅱ study on the treatment of RILI with pirfenidone is being carried out (NCT03902509), but no clinical study on the prevention has been reported. This is the first phase Ⅱ study designed to explore the efficacy of pirfenidone in preventing RILI.

Most published data on RILI was derived from lung cancer. However, differences in anatomy, pathogenesis, and treatment between lung and esophageal tumors limit the extrapolation of radiation pneumonitis (RP) prediction model of pulmonary tumors to esophageal tumors. This preliminary study was designed to focus on patients with

thoracic ESCC. Additionally, from the current NCCN guidelines and expert recommendations, tolerance dose-limits for lung vary from V20 of ≤20% for esophageal and esophagogastric junction cancers, and V20 of ≤35%-40% for non-small cell lung cancer. Obviously, esophageal cancer has more stringent restrictions on V20, which can be achieved by esophageal adenocarcinoma (EA) treatment plan, since it mainly presents in the lower thoracic area in European and American countries. But esophageal squamous cell carcinoma (ESCC),[50 51] highly prevalent in China and Asia, are often located in the upper or middle esophagus. Therefore, comparing to EA in which the RT area is close to the abdomen and the lung is relatively well protected, patients of thoracic ESCC is at risk of lung exposure and may require particular attention.[52] Consequently, the tolerance dose-limit of lung is recommended as V20≤28-30%, V5≤60%, and MLD 15 Gy[53] in the present study.

The estimated incidence of RILI varies widely across esophageal cancer studies from 3.33% to 35% of grade 2 lung injury, and 0% to 21% of grade 3 lung injury. It is likely due to variations of target delineation, radiation dose, radiotherapy techniques,[10-12 36 54-58] and classification systems. Since consensus of the optimal radiation strategy for nodal irradiation is lacking and accuracy of imaging diagnosis is insufficient[59] FDG-PET/CT at diagnosis is strongly recommended. Further, the elective nodal irradiation (ENI) is adopted depending on the location of the primary tumor.-Although the dose of 50 Gy is the standard for CCRT in most Western countries, 60 Gy dose using modern radiation technologies is more preferred by clinicians in Asian countries based on the belief that 50 Gy may not be enough for ESCC.[53 60 61] Consequently, 60 Gy dose to

PTV-GTV and 50.4 Gy dose PTV-CTV will be administered in the present study. However, only PTV-GTV or PTV-CTV irradiation is permitted when normal tissue constraints cannot be met by therapy, which is decided by the physician. Additionally, due to the anatomical features of esophagus, including the lack of serosa and the presence of numerous organs surrounding the esophagus, most patients in this trail have cT4N+M0 thoracic esophageal cancer. Till now, the standard treatment for the cT4N+M0 thoracic esophageal cancer has not been established, and therefore, definitive chemoradiotherapy (CRT) or chemoradiotherapy plus conversional surgery for down-staging patients are both accepted treatment.[61] The major difference between neoadjuvant and definitive CRT is the radiation dose (41.4 Gy VS. 50-60 Gy) which is the most crucial factor that influences the development of RILI. For this reason, stratified random cluster sampling is applied for balancing two groups.

Considering the anti-inflammatory and anti-fibrotic properties[16-18 43], the incidence of grade 2 or higher RILI is the primary endpoint to test the prevention of symptomatic RP and RF. As known, the diagnosis of RILI is challenging due to differential or concomitant diagnoses such as infections and exacerbation of pre-existing pulmonary conditions. Particularly， in some cases that pneumonia patches in the radiation beam pathway as well as RP complicated with infectious pneumonia could not be identified.[58] In addition, RP grading is limited by subjectivity especially in diagnosing grade 2 and grade 3. Therefore, the classification will be confirmed by a board-certified radiation oncologist referring to a joint expert consultation. The multidisciplinary team consists

of a senior radiation oncologist, a pulmonologist, and a radiologist with experience in RILI.

In summary, the present study design was endeavored to control for most of the important risk factors for RILI as describe above. The results might provide new options for the prevention of RILI. However, owing to the limited sample size, ~~further~~ research is required to substantiate the efficacy of pirfenidone for the prevention of RILI using a multicenter phase 3 trial with larger sample size.

List of abbreviations

AE: adverse event; AFP: α-fetoprotein; ALT: alanine transaminase; ANC: absolute neutrophil count; AST: aspartate transaminase; CA: cancer antigen; CBC: complete blood counts; CCr: creatinine clearance rate; CEA: carcinoembryonic antigen; CT: computed tomography; CTCAE : Common Terminology Criteria for Adverse Events; CTV: clinical target volume; Cyfra21-1: soluble fragment of cytokeratin 1; DFS: disease-free survival; Dmax: maximal dose; ECOG: Eastern Cooperative Oncology Group; ESCC: esophageal squamous cell carcinoma; FDG-PET/CT : [18F] fluorodeoxyglucose positron emission tomography/computed; FGF: fibroblast growth factor; FDA: Food & Drug Administration; GTV: gross tumor volume; HBV: hepatitis B virus; IL: interleukin; IMRT: intensity-modulated radiation therapy; IPF: idiopathic pulmonary fibrosis; MLD: mean lung dose;

NRS: nutritional risk scale; NSE: neuron-specific enolase; OAR: organs at risk; OS: overall survival; PDGF: platelet-derived growth factor; PEG-rhG-CSF: Polyethylene

glycol recombinant human granulocyte colony-stimulating factor; PTV: planned target volume; RILI: radiation-induced lung injury; RP: radiation pneumonitis; SCC: squamous cell carcinoma antigen; SCr: serum creatinine; TGF: tumor growth factor; TNF: tumor necrosis factor; ULN: upper limit of normal; WBC: white blood cells.

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Authors' contributions

XBH is the principal investigator responsible for study design, revised the article critically, and approved the final version to be published. Chen Cheng mainly participated in protocol design and writing. ZBW and YY are responsible for statistical and study design. Chen Chun and KMQ are responsible for surgery recommendation. XD, CRX, LSQ and ZHL made a substantial contribution to the design of the study. All authors read and approved the final manuscript.

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Competing interest statement

All authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). Signed informed consent from each participant is required. The trial was registered in chictr.org.cn (ChiCTR2100043032).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Not applicable – data collection is still ongoing.

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Figure legend

Figure 1. Flowchar of the study procedurest.

Table 1. Inclusion, exclusion and withdrawal criteria.

Inclusion criteria	Exclusion criteria	Withdrawal criteria
● Age between 18 and 75 years old. ● ECOG performance status of 0-1. ● Pathological confirmation of ESCC. ● Imaging staging suggests $T_{3\text{-}4}N+M0$ thoracic esophageal cancer according to AJCC 8 staging (primary lesions are mainly in the chest cavity). ● No restriction on the number of regional nodal stations or bulk of disease. ● Patients who cannot tolerate surgery or the tumor cannot be removed surgically.	● History of chest radiotherapy. ● Concomitant tumor in other organs or prior malignancies within 5 years. ● History of interstitial lung disease or non-infectious pneumonia including COPD. ● Severe cardiovascular disease, cerebrovascular complications, epilepsy, active peptic ulcers, infections, psychological disorders, or other serious underlying diseases	● Treatment delay for more than 2 weeks or interruption due to extended toxicity. ● Disease progression is judged by researchers during treatment.

● No perforation or deep niche in the esophageal cancer lesion. ● No prior chemotherapy, immunotherapy, or surgery before radiotherapy. ● Able to eat liquid food. ● Adequate bone marrow, liver, kidney, blood coagulation function, and lung functions. ● Life expectancy of >6 months. ● Voluntary participation in the study, with good compliance.	that may limit their understanding and tolerance of comprehensive treatments. ● Patients with a previous history of ataxia due to telangiectasia or other radiosensitivity reaction. ● Patients with scleroderma or active connective tissue disease.

ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; AJCC, American Joint Committee on Cancer; CT, computed tomography.

Table 2. Dose limits for organs at risk (OAR)

OAR	Normal Tissue Dose-Volume Constraints
Lung	V20 ≤28%-30%, V5 ≤60%; MLD <15 Gy
Heart	V40 <30%, V40 ≤30%; Mean ≤30 Gy
Spinal cord	Max ≤45 Gy
Stomach	V40 <40%, Max ≤55-60 Gy
Liver	V30 <40%; Mean ≤25 Gy

Vxx=% of the whole OAR receiving ≥xx Gy. Mld=mean lung dose

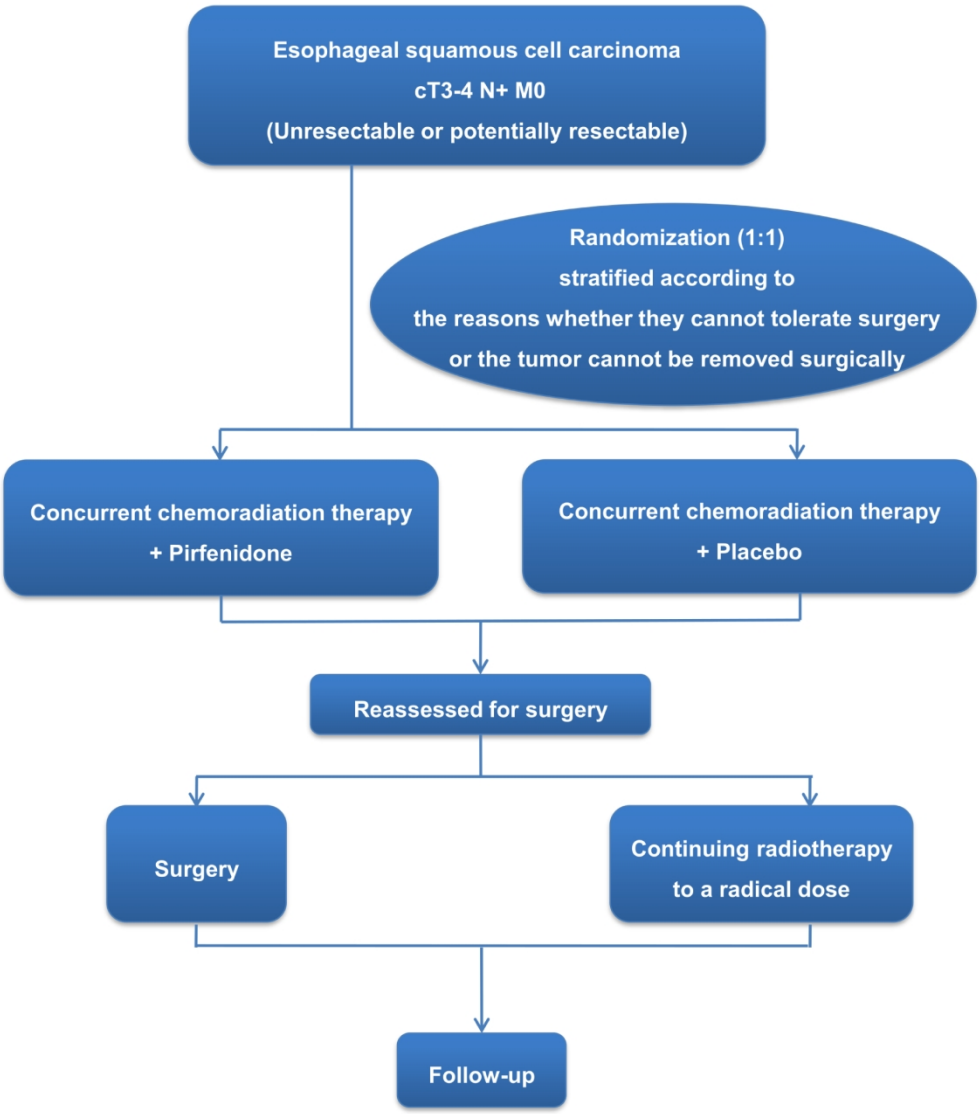

Figure 1. Study flowchart.

170x194mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,13
	5b	Name and contact information for the trial sponsor	/
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-9,Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	/
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	/
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	/
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6,9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	/
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	/
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	/
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	/
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A protocol for a randomized controlled trial

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Secondary Subject Heading:	Pharmacology and therapeutics, Respiratory medicine

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Pirfenidone for the prevention of radiation-induced lung injury in patients with locally advanced esophageal squamous cell carcinoma: A protocol for a randomized controlled trial

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Abstract

Introduction: Radiation-induced lung injury (RILI) is one of the most clinically-challenging toxicities and dose-limiting factors during and/or after thoracic radiation therapy for esophageal squamous cell carcinoma (ESCC). With limited effective protective drugs against RILI, the main strategy to reduce the injury is strict adherence to dose-volume restrictions of normal lungs. RILI can manifest as acute radiation pneumonitis (RP) with cellular injury, cytokine release, and cytokine recruitment to inflammatory infiltrate, and subsequent chronic radiation pulmonary fibrosis. Pirfenidone inhibits the production of inflammatory cytokines, scavenges free radicals, and reduces hydroxyproline and collagen formation. Hence, pirfenidone might be a promising drug for RILI prevention. This study aims to evaluate the efficacy and safety of pirfenidone in preventing RILI in patients with locally advanced ESCC receiving chemoradiotherapy.

Methods and analysis: This study is designed as a randomized, placebo-controlled, double-blinded, single-center phase 2 trial and will explore whether the addition of pirfenidone during concurrent chemoradiation therapy (CCRT) could prevent RILI in patients with locally advanced ESCC unsuitable for surgery. Eligible participants will be randomized at 1:1 to pirfenidone and placebo groups. The primary endpoint is the incidence of grade ≥2 RILI. Secondary endpoints include the incidence of any grade other than grade >2 RILI, time to RILI occurrence, changes in pulmonary function after CCRT, completion rate of CCRT, disease-free survival (DFS), and overall survival (OS). The follow-up period will be 1 year. In case the results meet the primary endpoint of this trial, a phase 3 multicenter trial with a larger sample size will be required to substantiate the evidence of the benefit of pirfenidone in RILI prevention.

Ethics and dissemination

This study was approved by the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). The findings of the trial will be disseminated through peer-reviewed journals, and national and international conference presentations.

Trial registration: ChiCTR2100043032

Strengths and limitations of this study

- This is the first randomized controlled trial to explore the efficacy and safety of pirfenidone in RILI prevention.
- It is a double-blinded trial where neither patients nor physicians will know the treatment allocation.
- It is a phase 2 trial performed at a single center.
- The dosage of radiation is usually inconsistent, with patients with unresectable patients receiving 50 Gy to 60 Gy, and cases in the process of downstaging receiving 40 Gy due to further option of surgical resection.

Key words: Pirfenidone; radiation-induced lung injury; prevention; esophageal squamous cell carcinoma; concurrent chemoradiation therapy; randomized controlled trial.

Introduction

Esophageal cancer is the eighth most common cancer worldwide. Of the 477,900 new cases reported globally per year, nearly half occur in China, and 90% of them are ESCC.[1] The definitive standard of care for unresectable locally advanced ESCC remains concurrent chemoradiation therapy, with a 3-year OS rate of 30%-37%.[2-5] Because the lungs often lay in the path of treatment radiation beams, radiation-induced lung injury (RILI) is inevitable. RILI is one of the most common side effects and potentially dose-limiting toxicities of radiotherapy for esophageal cancer, with an incidence of about 10.7%-35.14%.[6-11] Furthermore, RILI during radiation can delay or even interrupt radiotherapy, resulting in poor local control of the disease, increased financial burden, and even death.

Although advanced radiotherapeutic technologies such as intensity-modulated radiation therapy (IMRT) are superior to traditional 2D and 3D conformal radiation therapies regarding dosimetry and organ protection,[10 12] many patients still develop varying degrees of RILI.[13] In clinical practice, there is no specific treatment for RILI except oxygen inhalation, glucocorticoid administration, and the application of antibiotics when necessary. Therefore, preventing RILI is of greater clinical significance than treating it. Although amifostine was approved by the US Food & Drug Administration (FDA) for radiotherapy protection, it does not efficiently protect against RILI during esophageal cancer treatment.[14 15] Moreover, its clinical application is limited because of high cost and frequent side effects. Therefore, few effective protective strategies against RILI during radiotherapy are available for patients with ESCC.

Pirfenidone is an active small-molecule oral drug that inhibits transforming growth factor (TGF)-β1 overexpression and reduces the secretion of platelet-derived growth

factor (PDGF) and fibroblast growth factor (FGF), thereby suppressing the biological activity of fibroblasts.[16-18] Pharmacodynamic studies have demonstrated pirfenidone exerts satisfactory effects in lung inflammation and fibrosis.[19-22] The FDA approved pirfenidone in 2014 for the treatment of idiopathic pulmonary fibrosis (IPF),[23 24] which shares some pathological manifestations with RILI.[25 26] A previous study in mice showed pirfenidone attenuates RILI.[27] A phase 2 trial is in the recruitment stage and aims to confirm the efficacy of pirfenidone in the treatment of RILI (ClinicalTrials.gov NCT03902509).

There are no published clinical data to assess the prophylactic role of pirfenidone in RILI. Therefore, this randomized, placebo-controlled, double-blinded, single-center, phase 2 trial is designed to examine whether pirfenidone could reduce the occurrence of RILI in patients with locally advanced ESCC administered CCRT.

Methods

Study design and participants

This is a randomized, placebo-controlled, double-blinded, single-center, phase 2 clinical trial to examine the potential of pirfenidone in preventing RILI in patients with unresectable locally advanced ESCC at diagnosis administered CCRT. The participants will be randomized at 1:1 to the pirfenidone and control groups. Figure 1 depicts the overview of the study procedure.

The detailed inclusion, exclusion, and withdrawal criteria are listed in Table 1.

All eligible patients should provide written informed consent and be willing to participate in and complete the study, including follow-up.

Pre-treatment assessment and screening

Each patient must complete the following examinations and undergo counseling within 1 or 2 weeks before the onset of the trial:

1) Detailed medical history review.

2) Physical examinations to record height, weight, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.

3) Blood tests, including complete blood count (CBC), serum biochemistry, coagulation function, hepatitis B virus (HBV) and HBV DNA (for HBsAg-positive patients), and esophageal cancer-related tumor markers such as carcinoembryonic antigen (CEA), cancer antigen (CA) 199, CA125, CA153, neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCC), soluble fragment of cytokeratin 19 (Cyfra21-1), and α-fetoprotein (AFP).

4) Cardiopulmonary function evaluation, including electrocardiography, ultrasonic cardiography, and pulmonary function assessment.

5) Upper gastrointestinal endoscopy and biopsy.

6) Imaging, including chest/abdominal computed tomography (CT) with intravenous contrast and upper gastrointestinal swallowed meglumine diatrizoate contrast, pelvic CT with contrast as clinically indicated, and $^{[18F]}$fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) if accepted by the patient, leading to more accurate staging.

7) Nutritional assessment and counseling.

8) Smoking cessation counseling.

Radiotherapy

The target contour principle is as follows. Gross tumor volume (GTV) includes the primary tumor (GTVp) and enlarged regional lymph nodes (GTVn), determined by CT simulation scan and other diagnostic imaging methods. Elective node irradiation (ENI) will be used for clinical target volume (CTV) delineation. CTV of GTVp is defined as primary tumor volume plus a superior-inferior 3cm margin expansion and a 0.5-1-cm radial expansion including para-esophageal lymph nodes. CTV of GTVn will cover all the lymph nodes involved and high-risk lymphatic drainage regions such as the supraclavicular region for super-thoracic and middle-thoracic sections.[28] Planning target volume (PTV) for GTV and CTV will be created by expanding with a uniform margin of 0.5 cm separately. The recommended doses for PTV-CTV and PTV-GTV are 50.4 Gy/1.8 Gy/28 fractions and 60 Gy/1.8 Gy/33 fractions, respectively. If the target area is large and OAR cannot be achieved, only PTV-GTV irradiation or PTV-CTV irradiation can be performed as determined by the treating radiotherapist. The administered dose should cover at least 95% of the PTV. Normal tissue tolerance dose-limits are listed in Table 2. All patients will be positioned supine on the treatment couch and fixed with a custom-fitted thermoplastic sheet, and setup imaging will be acquired every day before treatment to correct the treatment position by the On-board imaging (OBI) image system. IMRT is recommended when the treatment plans are designed. Dose calculation for areas with artifacts generates heterogeneity, leading to high dose deviation. To ensure the quality of the radiotherapy delivered, the Acuros XB (version

15.5) dose algorithm that was reported to be as accurate as or close to the Monte Carlo (MC) simulation method will be employed in this present study. The treatment plan for all patients will be verified using the Delta4 Phantom, and the gamma passing rate at the criteria of 3%/3 mm will be greater than 98%.

Resectability will be re-assessed by a multidisciplinary team at irradiation with 41.4 Gy. If surgical resection is possible, radiation therapy will be discontinued, and surgery will be performed 4-8 weeks after radiation termination.

Chemotherapy

The participants will receive docetaxel at 60 mg/m^2 intravenously on day 1 and cisplatin at 30 mg/m^2 intravenously on days 1 and 2 for two cycles. Polyethylene glycol recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is recommended for the prevention of neutropenia during CCRT. Dose modification will be based on the preceding cycle's CBC data and biochemical markers. Chemotherapy will be continued with: 1) absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L; 2) platelet count $\geq 100\times10^9$/L; 3) grade <2 alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin based on Common Terminology Criteria for Adverse Events (CTCAE) criteria; 4) non-hematological toxicity (except for hair loss) returning to grade 1 or baseline level. The doses of both drugs will be decreased by 20% in case of any grade 3 or higher toxicities. In case of grade 3 or 4 radiation pneumonitis, radiotherapy and concurrent chemotherapy will be terminated.

Randomization and intervention

The participants will be randomized at 1:1 to the pirfenidone or control groups

using a random number table and stratified based on tolerability or ineligibility to surgery. Participants and doctors will be blinded to treatment allocation. Identical pirfenidone and placebo capsules will be provided by Beijing Continent Pharmaceutical Co., Ltd. The appearance, smell, taste, and properties of the placebo are the same as those of the study drug. Each capsule contains 100 mg of drug or placebo. In the first week, the dosage will be 200 mg/time, 3 times/day. In the second week, the dosage will be increased to 300 mg/time, 3 times/day. In weeks 3-12, the dosage will be further increased to 400 mg/time, 3 times/day. Pirfenidone treatment will start on the day of radiotherapy initiation and last for 12 weeks. The capsules will be taken during or after meals as gastrointestinal reactions are the most common adverse effects of pirfenidone. Photosensitivity is another common adverse event. External use of sunscreen and avoiding the sun during medication can effectively reduce the incidence and severity of photosensitivity reactions. In case adverse events still occur or cannot be tolerated even after dose reduction, the drug will be temporarily discontinued for 1-2 weeks until the participant tolerates the symptoms. Once adverse events are alleviated or can be tolerated, the participant will retake pirfenidone. The physician can decide whether to stop the drug treatment according to the situation. Pirfenidone treatment will be permanently discontinued in case of severe adverse events, including liver dysfunction, jaundice, severe hypersensitivity, and photosensitivity.

Concomitant medication

Drugs that may prevent or treat fibrosis are forbidden, including amifostine and thalidomide. The participants should avoid the concurrent use of drugs that increase the adverse reactions of pirfenidone, including ciprofloxacin, amiodarone and propafenone. The participants should also avoid concurrent administration of medications that can

reduce the efficacy of pirfenidone, including omeprazole and rifampin.

Endpoints

The primary endpoint is the incidence of grade 2 or higher RILI in the full analysis set (FAS) and per-protocol set (PPS). RILI will be evaluated according to CTCAE version 5.0.[29] within 1 year. Secondary endpoints include the incidence of RILI of any grade, time to RILI occurrence, pulmonary function changes after radiotherapy, completion rate of CCRT, DFS and OS.

RLIL is a diagnosis established based on clinical suspicion or radiological findings after excluding other lung pathologies such as pre-existing pathologies and pulmonary infection. It often occurs with no specific symptom, altered vital signs, laboratory profiling or imaging findings. The familiar history of radiation and recognition of RILI are of utmost importance in the context of regular follow-up. Diagnosis and grading will be confirmed after review by multidisciplinary senior physicians, including a radiation oncologist, a pulmonologist, and a radiologist. Medical history, physical parameters, chest CT scans, and previous radiotherapy will be evaluated at every follow-up during personal visits when available. RILI will be scored based on the CTCAE version 5.0 classifying symptoms and imaging findings will be used to classify into five grades[29] For symptoms, dyspnea and dry cough are the most common manifestations-in acute lung injury.[30] Occasional fever is usually mild, but high fever is sometimes reflective of co-infectious pneumonitis. Chronic radiation fibrosis (RF) is a slowly progressing respiratory disease that can manifest as respiratory insufficiency. In terms of physical symptoms, physical examination findings may be normal or

include pleural rub, moist rales, and signs of consolidation. Chest imaging, particular lung CT at baseline and follow-up are critical in the diagnosis and grading. In the acute phase, which usually appears 4-8 weeks after radiotherapy, CT images may display exudative changes such as multiple small patchy or flock-shaped ground glass density shadows in the irradiation field, with fuzzy edges and unclear boundaries with surrounding lung tissue. In the consolidation phase, which usually occurs 2-3 months after radiotherapy, CT images may display patchy high-density consolidations in the irradiation field, not distributed according to the lung lobe or lung segment, accompanied by partial air bronchial signs. In the fibrotic stage, which usually occurs six months after radiotherapy, CT images may show density enhancement shadows of grid, cord, or patchy shape in the irradiation field with clear boundaries, accompanied by thickened pleura, lung volume reduction, lung hilum reduction, ipsilateral vascular texture thinning, and compensatory increase in contralateral lung volume.[31-35]

Considering the anti-inflammatory and anti-fibrotic properties of pirfenidone, the grade will be scored at the maximal level in cases who experience RP and RF. When one case shows grade 3 RP and grade 2 RF, grade 3 will be recorded for the primary endpoint. As pirfenidone is a promising drug for the prevention of RP and RF, we chose 1 year to observe the rates of RP and RF.

Follow-up

1. During the intervention period.

1) CBC and biochemical profiles will be verified once a week.

2) Physical examination and nutritional score assessment will be performed once a week.

3) Pulmonary function and chest/abdominal CT will be performed after 23 fractions to assess tumor regression and eligibility for surgery.

2. Post-treatment

The follow-up period will be 1 year or until death. All participants will be followed up at 1 month after radiotherapy and every 3 months thereafter, or as needed clinically. Routine follow-up will include the assessment of clinical symptoms, CBC and tumor markers, contrast-enhanced CT and upper gastrointestinal contrast, and pulmonary function evaluation. Repeated gastroscopy is recommended for the first year. In case of suspected recurrence, physical examination, radiography, and pathological examination will be performed.

Statistical analysis

Based on retrospective studies in the authors' hospital and literature reviews,[7 8 36-38] it is assumed that the occurrence rate of grade ≥2 RILI in the control group is 25%, versus 10% in the pirfenidone group. This trial is designed as a randomized phase 2 study with a two-sided α of 0.20 and a power of 80%,[39] using the PASS software version 15.0.5 to calculate the sample size. From a phase 2 screening design, a higher α level than 0.05 will be used for the next phase 3 design. Even if the phase 2 trial is successful, such a positive result is not usually considered to be definitive without a subsequent phase 3 trial. In this study, 36 participants will be included in each group with an α-level of 0.2 and a power of 80%. Considering a dropout rate of 20%, it is planned to

enroll about 88 participants.

All analyses will be performed with SAS version 9.3 (SAS Institute, Cary, NC, USA). The t-test will be used for analyzing continuous data. The chi-square test and Fisher's exact probability method will be used for comparing categorical data. The survival rate will be calculated by the Kaplan-Meier method, and between-group comparisons will use the log-rank test. The confidence interval of the survival distribution will be calculated according to Greenwood's formula. A proportional hazard regression model for risk estimation will be used to derive hazard ratios. $P<0.05$ will be considered statistically significant.

Data collection and management

All clinical data will be collected by a research assistant and recorded in detail in the predesigned electronic table. All written informed consent forms will be stored in a separate closet, and only researchers would access the relevant research data. All study procedures were developed to ensure data protection and confidentiality.

Dissemination

The results will be disseminated in international peer-reviewed conferences and journals.

Patient and public involvement

Patients and the public are not involved in the design or execution of the study or the outcome measures.

Discussion

For many years, radiotherapy (RT) has been employed for the treatment of esophageal cancer as a curative or palliative measure. However, RILI is a common and severe side effect of radiation, which can delay or interrupt antitumor therapy, resulting in poor local control of the disease, decreased quality of life, and even death. Therefore, prophylactic drugs to minimize toxicity and maximize efficacy in RT are required. To date, the only FDA-approved cytoprotective agent is amifostine, but limited effectiveness and significant side effects hamper its clinical application.[14, 15, 34, 35] Consequently, pharmaceutical agents that are clinically applicable, especially for the prevention of RILI are being developed[40-42] Pirfenidone is a small-molecule biosynthetic drug with anti-inflammatory, anti-fibrotic, and antioxidant properties,[16-18 43] which was approved by the FDA for the management of IPF.[23 24 44-46] As RILI has similar pathogenesis and clinical manifestations as IPF, characterized by inflammatory cell infiltration, interstitial edema, and interstitial fibrosis of the alveolar wall,[26] pirfenidone may hold promise for the prevention and treatment of RILI, which has been tested in preclinical and pilot studies.[47, 27, 48, 49] Currently, a multicenter phase Ⅱ study on the treatment of RILI with pirfenidone is ongoing (NCT03902509), but no clinical study on the prevention has been reported. This is the first phase Ⅱ study designed to explore the efficacy of pirfenidone in RILI prevention.

Most published data on RILI were derived from lung cancer. However, differences in anatomy, pathogenesis, and treatment between lung and esophageal tumors limit the extrapolation of RP prediction models for pulmonary tumors to esophageal tumors. This preliminary study was designed to focus on thoracic ESCC. Additionally, from the

current NCCN guidelines and expert recommendations, tolerance dose-limits for the lung vary from V20 ≤20% for esophageal and esophagogastric junction cancers, and V20 ≤35%-40% for non-small cell lung cancer. Obviously, esophageal cancer has more stringent restrictions on V20, which can be achieved by esophageal adenocarcinoma (EA) treatment plan, since it is mainly present in the lower thoracic area in European and American countries. But esophageal squamous cell carcinoma (ESCC),[50 51] highly prevalent in China and other Asian countries, is often located in the upper or middle esophagus. Therefore, compared to EA cases in whom the RT area is close to the abdomen and the lung is relatively well protected, patients with thoracic ESCC are at higher risk of lung exposure and may require particular attention.[52] Consequently, the recommended tolerance dose-limits of the lung are V20≤28-30%, V5≤60%, and mean lung dose（MLD）<15 Gy[53] in the present study.

The estimated incidence of RILI varies widely across esophageal cancer studies from 3.33% to 35% for grade 2 lung injury, and 0% to 21% for grade 3 lung injury. It is likely due to variations of target delineation, radiation dose, radiotherapy techniques,[10-12 36 54-58] and classification systems. Since consensus on the optimal radiation strategy for nodal irradiation is lacking and the accuracy of imaging diagnosis is insufficient,[59] FDG-PET/CT at diagnosis is strongly recommended. Further, ENI is adopted depending on the location of the primary tumor. Although the dose of 50 Gy is the standard for CCRT in most Western countries, 60 Gy using modern radiation technologies is preferred by clinicians in Asian countries based on the belief that 50 Gy may not be enough for ESCC.[53 60 61] Consequently, 60 Gy for PTV-GTV and 50.4 Gy

for PTV-CTV will be administered in the present study. However, only PTV-GTV or PTV-CTV irradiation is allowed when normal tissue constraints cannot be met by therapy, which is decided by the physician. Additionally, due to the anatomical features of the esophagus, including the lack of serosa and the presence of numerous surrounding organs, most patients in this trial have cT4N+M0 thoracic esophageal cancer. Until now, a standard treatment option for cT4N+M0 thoracic esophageal cancer has not been established, and therefore, definitive chemoradiotherapy (CRT) or chemoradiotherapy plus conversional surgery for downstaging are both accepted treatments.[61] The major difference between neoadjuvant and definitive CRT is the radiation dose (41.4 Gy vs. 50-60 Gy), which is the most crucial factor affecting the development of RILI. For this reason, stratified random cluster sampling will be applied for balancing the two groups.

Considering anti-inflammatory and anti-fibrotic properties[16-18 43], the incidence of grade 2 or higher RILI is the primary endpoint to test in the prevention of symptomatic RP and RF. The diagnosis of RILI is challenging due to differential or concomitant diseases such as infections and exacerbation of pre-existing pulmonary conditions. Particularly，in some cases pneumonia patches in the radiation beam pathway as well as RP complicated with infectious pneumonia could not be identified.[58] In addition, RP grading is limited by subjectivity, especially in diagnosing grade 2 and grade 3. Therefore, the classification will be confirmed by a board-certified radiation oncologist referring to a joint expert consultation. The multidisciplinary team consists of a senior radiation oncologist, a pulmonologist, and a radiologist with broad experience in RILI.

In summary, the present study design attempted to control for most of the important risk factors for RILI as described above. The results might provide new options for the prevention of RILI. However, owing to the limited sample size, further research is required to substantiate the efficacy of pirfenidone in the prevention of RILI using a multicenter phase 3 trial with a larger sample size.

List of abbreviations

AE, adverse event; AFP, α-fetoprotein; ALT, alanine transaminase; ANC, absolute neutrophil count; AST, aspartate transaminase; CA, cancer antigen; CBC, complete blood counts; CCr, creatinine clearance rate; CCRT, concurrent chemoradiation therapy; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; Cyfra21-1, soluble fragment of cytokeratin 1; DFS, disease-free survival; Dmax, maximal dose; EA, esophageal adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; ENI, elective node irradiation; ESCC, esophageal squamous cell carcinoma; FAS： full analysis set; FDG-PET/CT ： [18F] fluorodeoxyglucose positron emission tomography/computed; FGF, fibroblast growth factor; FDA, Food & Drug Administration; GTV, gross tumor volume; HBV, hepatitis B virus; IL, interleukin; IMRT, intensity-modulated radiation therapy; IPF, idiopathic pulmonary fibrosis; MC, Monte Carlo; MLD, mean lung dose; NRS, nutritional risk scale; NSE, neuron-specific enolase; OAR, organs at risk; OBI, On-board imaging; OS, overall survival; PDGF, platelet-derived growth factor; PEG-rhG-CSF, Polyethylene glycol recombinant human granulocyte colony-stimulating factor; PPS：per-protocol

set; PTV, planned target volume; RF, radiation fibrosis; RILI, radiation-induced lung injury; RP, radiation pneumonitis; RT, radiotherapy; SCC, squamous cell carcinoma antigen; SCr, serum creatinine; TGF, tumor growth factor; TNF, tumor necrosis factor; ULN, upper limit of normal; WBC, white blood cells.

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Authors' contributions

XBH, the principal investigator responsible for the study design, also revised the article critically and approved the final version to be published. CC mainly participated in protocol design and writing. ZBW and YY were responsible for statistical analysis and study design. CC and KMQ were responsible for surgery recommendation. XD, CRX, LSQ and ZHL made substantial contributions to the design of the study. All authors read and approved the final manuscript.

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Competing interest statement

All authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Fujian Union Hospital (No. 2021YF001-02). Signed informed consent from each participant is required. The trial was registered in chictr.org.cn (ChiCTR2100043032).

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Not applicable – data collection is still ongoing.

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Figure legends

Figure 1. Flowchart of the study procedure.

Table 1. Inclusion, exclusion and withdrawal criteria.

Inclusion criteria	Exclusion criteria	Withdrawal criteria
● Age between 18 and 75 years old. ● ECOG performance status of 0-1. ● Pathological confirmation of ESCC. ● Imaging staging suggesting $T_{3-4}N+M0$ thoracic esophageal cancer according to AJCC 8 staging criteria (primary lesions mainly in the chest cavity). ● No restriction on the number of regional nodal stations or bulk of disease. ● No ability to tolerate surgery or tumor not surgically removable.	● History of chest radiotherapy. ● Concomitant tumor in other organs or prior malignancies within 5 years. ● History of interstitial lung disease or non-infectious pneumonia including COPD. ● Severe cardiovascular disease, cerebrovascular complications, epilepsy, active peptic ulcers, infections, psychological disorders, or other serious underlying diseases	● Treatment delay for more than 2 weeks or interruption due to extended toxicity. ● Disease progression as judged by researchers during the treatment.

● No perforation or deep niche in the esophageal cancer lesion. ● No prior chemotherapy, immunotherapy, or surgery before radiotherapy. ● Ability to eat liquid foods. ● Adequate bone marrow, liver, kidney, blood coagulation, and lung functions. ● Life expectancy of >6 months. ● Voluntary participation in the study, with good compliance.	that may limit the patient's understanding and tolerance of comprehensive treatments. ● A previous history of ataxia due to telangiectasia or other radiosensitivity reaction. ● Scleroderma or active connective tissue disease.

ECOG, Eastern Cooperative Oncology Group; ESCC, esophageal squamous cell carcinoma; AJCC, American Joint Committee on Cancer; CT, computed tomography.

Table 2. Dose limits for organs at risk (OAR)

OAR	Normal Tissue Dose-Volume Constraints
Lung	V20 ≤28%-30%, V5 ≤60%; MLD <15 Gy
Heart	V40 <30%, V40 ≤30%; Mean ≤30 Gy
Spinal cord	Max ≤45 Gy
Stomach	V40 <40%, Max ≤55-60 Gy
Liver	V30 <40%; Mean ≤25 Gy

Vxx, % of the whole OAR receiving ≥xx Gy. MLD, mean lung dose

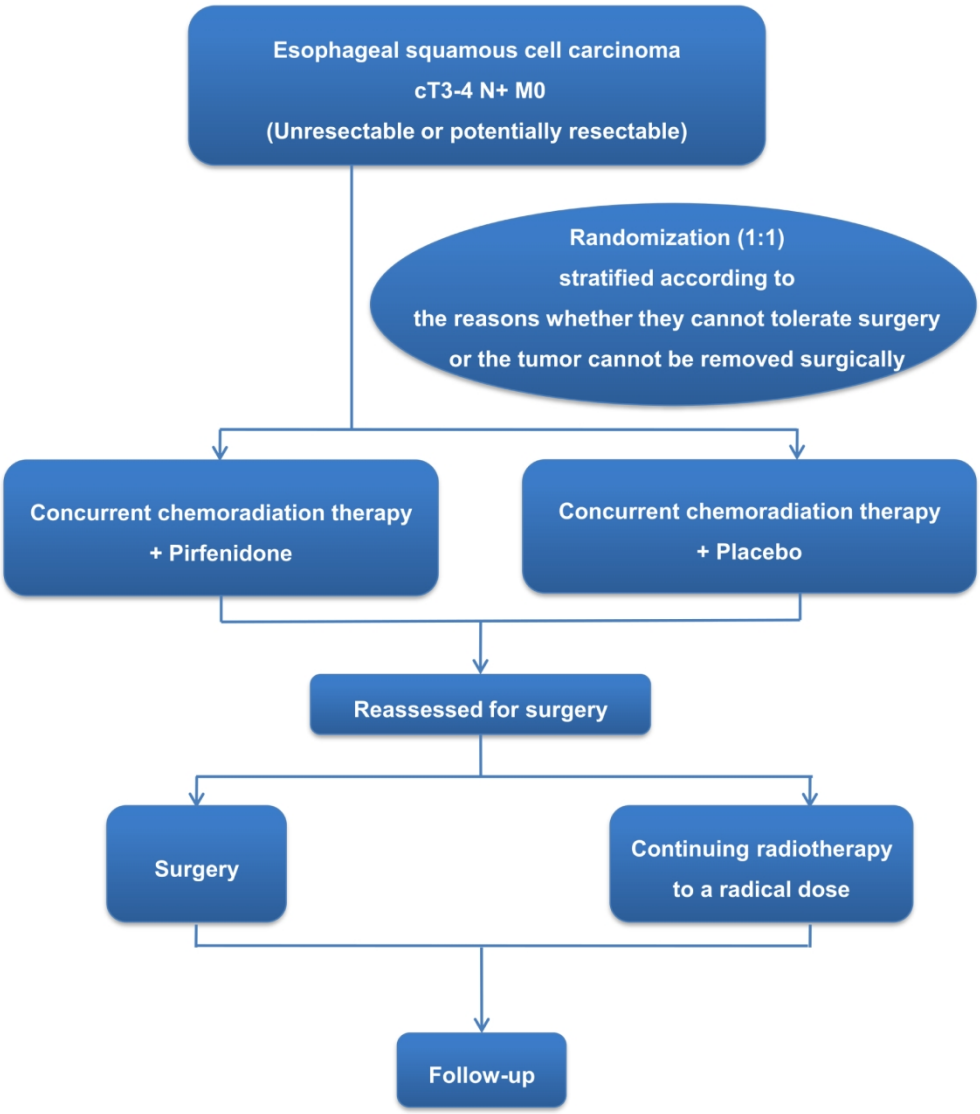

Figure 1. Study flowchart.

170x194mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	/
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2,13
	5b	Name and contact information for the trial sponsor	/
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13,14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13,14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5-9,Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	/
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	/
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	/
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-6,9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	/
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	/
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	/
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	/
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	/
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	/

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	/
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	/
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.