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Efficacy and safety of concurrent programmed cell death protein 1 inhibitor and definitive radiotherapy with immunonutrition support in esophageal squamous cell cancer: a phase II multicenter clinical trial

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Abstract

Background Esophageal cancer is one of the most common malignant tumors, with China accounting for 50% of the world's total incidence. Concurrent chemoradiotherapy (cCRT) with platin-based dual-drug regimen is the standard treatment for inoperable, locally advanced esophageal cancer in patients with a good performance status. However, certain patients possess risk factors that heighten toxicity and reduce their tolerance to cCRT, thereby challenging the feasibility of standard treatment. This study evaluates an alternative therapeutic approach combining programmed cell death protein 1 inhibitor (PD-1 inhibitor), definitive radiotherapy, and immunonutrition support for patients with unresectable non-metastatic esophageal cancer expressing PD-L1 who are intolerant to cCRT.

Methods This is a phase II, single-arm, multicenter clinical trial involving patients with histologically confirmed unresectable esophageal squamous cell carcinoma (ESCC), who exhibit positive PD-L1 and are unsuitable for cCRT. Participants will receive a total radiotherapy dose of 50–60 Gy in 25–30 fractions, sintilimab (200 mg every three weeks), alongside, supplemented by enteral nutritional emulsion (600–1600 ml/day). The primary endpoint is the 1-year progression-free survival rate, with secondary endpoints including objective response rate, overall survival and incidence of adverse events.

Conclusion This research has the potential to redefine treatment for inoperable ESCC patients who cannot tolerate conventional therapies. By evaluating a less toxic regimen that combines immunotherapy, radiotherapy, and nutritional support, we aim to determine if this approach can improve both survival rates and quality of life. The synergistic effects of immunonutrition support and PD-1 inhibitor will also be explored.

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Keywords ESCC, Sintilimab, Radiotherapy, Immunonutrition, Clinical trial

Background

Esophageal cancer, a devastating malignancy with a disproportionately high incidence in China, presents a significant global health challenge [1]. The squamous cell carcinoma (ESCC) subtype, prevalent in China, often diagnosed at the middle or locally advanced (LA) stage, resulting in a poor prognosis with only a 20% 5-year overall survival rate [1, 2]. More than half of these patients are not suitable for surgery, making definitive concurrent chemoradiotherapy (cCRT) the standard curative treatment. However, some patients, particularly those who are malnourished, elderly, or have pre-existing conditions, are unable to tolerate cCRT due to its associated toxicity [3]. This unmet need underscores the urgency of developing alternative therapeutic strategies that are both potent and well-tolerated.

Immune checkpoint inhibitors (ICIs), particularly programmed cell death protein 1 (PD-1) inhibitor, have significantly advanced the treatment of metastatic esophageal cancer, improving both overall survival and progression-free survival in patients [4–8]. Recent preclinical studies have highlighted the potential synergistic effects of combining immunotherapy with radiotherapy, showing enhanced tumor regression compared to radiotherapy alone [9, 10]. This combination therapy is particularly effective in patients with positive PD-L1 expression and has shown promising results in clinical trials for patients with locally advanced non-small cell lung cancer (NSCLC), achieving longer progression-free survival compared to cCRT [11, 12]. However, clinical evidence on the use of single-agent immunotherapy in conjunction with radiotherapy for ESCC remains scarce, especially in the context of PD-L1 positive tumors.

To address this issue, we started a single-arm trial evaluating the efficacy and safety of concurrent immunotherapy (sintilimab) plus definitive radiotherapy with immunonutrition support (enteral nutritional emulsion (TPF-T) followed by consolidation immunotherapy in patients with inoperable ESCC, who are PD-L1 positive expressed and intolerant to cCRT. The aim of current trial is to determine whether the current treatment regimen could offer comparable outcomes as cCRT.

Methods and study design

Study design and participants

This is a prospective, single-arm, phase II clinical trial designed to evaluate the efficacy and safety of sintilimab plus definitive radiation therapy for PD-L1-positive unresectable ESCC (Fig. 1). Patients eligible for enrollment were adults (≥ 18 years) with a histologically confirmed diagnosis of locally advanced or early stage ESCC deemed unresectable and unsuitable for cCRT by a multidisciplinary team, with no history of prior systemic therapy. Additionally, inclusion criteria mandated a PD-L1 tumor proportion score (TPS) or combined positive score (CPS) of at least 1%, as assessed by the 22C3 pharmDx assay, and the presence of at least one measurable lesion according to RECIST v1.1. Participants were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and an estimated life expectancy of more than 3 months. To ensure safety, adequate organ function was also a prerequisite. Conversely, patients were excluded if they presented a high risk of bleeding or perforation due to tumor invasion of adjacent organs or fistula formation. A history of prior malignancy (excluding certain non-melanoma skin cancers) within 3 years, previous systemic immunological therapy (except for localized pleural effusion management), or previous chest radiotherapy were additional exclusion criteria.

Treatments

Interventions consist of 50–60 Gy in 25–30 fractions of radiotherapy and 200 mg of sintilimab (PD-1 inhibitor) administered three times weekly, along with enteral nutritional emulsion (TPF-T) support (600–1600 ml per day according to the nutrition status evaluation). The administration of sintilimab will continue until disease progression, death, intolerable toxicity, withdrawal of informed consent, initiation of new anti-tumor treatment, or termination of treatment for other reasons as stipulated by the protocol.

Endpoints and assessments

The primary objective of this clinical trial is to evaluate the efficacy of combination of PD-1 inhibitor and definitive radiotherapy with immunonutrition support. The primary endpoint is the one-year progression-free survival (PFS) rate, as determined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints include objective response rate (ORR) and the duration of PFS until disease progression or death. Objective tumour assessments are performed by independent central review and investigators in accordance with RECIST v1.1. The staging assessments include neck/chest/abdominal/pelvic CT and magnetic resonance imaging (MRI) of brain, gastroscope, and radionuclide bone. Positron emission tomography (PET)-CT was recommended but not mandatory. Follow-up is conducted at baseline and every 8 weeks in the first year,12 weeks in

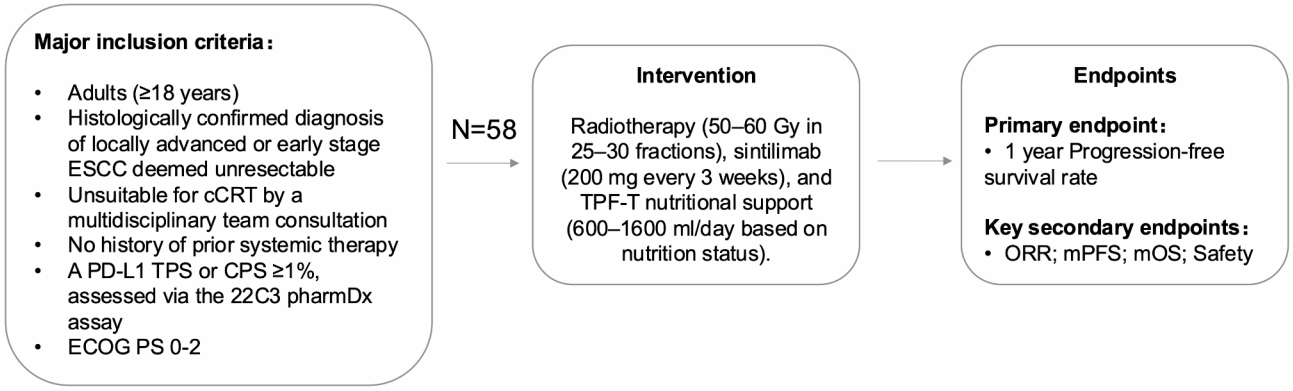

Fig. 1 Study design and schema

the second year and every 24 weeks from the third to fifth year, until progression or for five years post-treatment initiation.

The safety and tolerability will be rigorously monitored throughout the trial, with adverse events (AEs). Safety variables include symptoms, vital signs, physical examinations, evaluation of changes to concomitant medications, clinical laboratory parameters (hematology, serum chemistry), and the incidence, timing and severity of AE. AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Expression of PD-L1 in fresh or archival tumor sample was assessed during screening period with the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA). The tumour proportion score was defined as the percentage of the number of viable tumor cells showing partial or complete membrane staining. The combined positive score was defined as the percentage of the number of all PD-L1–expressing cells (tumor cells, lymphocytes, macrophages) to the number of all tumor cells. Tumor microenvironment and peripheral blood were monitored at baseline and after 40 Gy radiation for association with efficacy. Tumor biopsies and peripheral blood mononuclear cells will be collected at two key time points to facilitate transcriptomic profiling. Baseline samples will be obtained prior to the initiation of treatment to establish a reference for molecular analysis. Post-treatment samples will be collected after the completion of radiotherapy at a dose of 40 Gy or at the time of disease progression, whichever occurs first.

Sample size

We hypothesize that the addition of a PD-L1 inhibitor to radiotherapy will increase the 1-year progression-free survival (PFS) rate from 40% [13–15] to 60% [13, 15–17]. A total of 58 patients are necessary to detect a 20% improvement of 1-year PFS rate with 80% power at a one-sided type error of 0.025.

Trial status

This study protocol was finalized on August 18, 2023, as Version 2023 v1.0, and subsequently amended on February 1, 2024, as Version 2024 v1.0. Recruitment for the trial began on December 1, 2023, at multiple participating centers across China. The planned sample size for the study is 58 patients, and we anticipate completing patient enrollment by December 2026.

Ethical considerations

This study adheres to the ethical principles set forth in the Declaration of Helsinki and the International Ethical Guidelines of the Council for International Organizations of Medical Sciences. All participants will provide written informed consent prior to their inclusion in the study. Ethical approval has been granted by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital, affiliated with the Chinese Academy of Medical Sciences and Peking Union Medical College (Study ID: NCC4409). The study's protocol is registered on ClinicalTrials.gov under the identifier NCT06342167.

Discussion

Esophageal cancer is one of the most common malignant tumors, with China accounting for 50% of the world's total incidence, of which squamous cell carcinoma accounts for over 90%. Recent study has reinforced the standard management of LA-ESCC. However, it still resulted in high local recurrence rates of approximately 50% and 3-year PFS < 50% [16–19]. For patients who decline or are ineligible for cCRT, radiotherapy (RT) alone is the preferred alternative, but 1-year progression-free survival (PFS) rate was only about 40% [13–15]. Therefore, new treatment options are required for this population of patients. This study was designed to evaluate the efficacy and safety of an alternative by combining immunotherapy (sintilimab) and definitive radiotherapy with immunonutrition support (enteral nutritional

emulsion (TPF-T)) for inoperable ESCC patients with PD-L1 positive expression and intolerant to cCRT.

The synergistic effects of combining immunotherapy with radiotherapy have been proved in both basic and clinical studies. In mechanism research, radiotherapy induces immunogenic cell death in cancer cells, leading to the release of tumor-associated antigens. These antigens are captured by antigen-presenting cells and then presented to T cells, effectively creating an "in situ vaccine" that activates a systemic adaptive immune response to eradicate tumors [20, 21]. Additionally, radiotherapy modifies the tumor microenvironment by increasing the expression of PD-L1 and altering the levels of various cytokines and chemokines. This transformation changes immunologically "cold" tumors into "hot" tumors, making them more receptive to immunotherapy [22, 23]. ICIs complement this by activating cytotoxic T cells to target tumor cells and normalizing tumor vasculature, which enhances tissue perfusion, reduces tumor hypoxia, and increases the tumor's sensitivity to radiotherapy [24, 25]. In clinical treatment, integration of immune checkpoint inhibitors (ICIs) with RT has shown promise, particularly in phase I/II trials in LA-ESCC [18, 26]. ICIs alone was reported with clinical response rates of 22–33% and a median PFS of 1.8–3.6 months in advanced esophageal cancer patients [5, 27–30]. However, when combined with radiotherapy, the median PFS was increased to 12.2 months and the one-year OS rate stood at 78.4% (95% CI, 66.9 to 92.0), with the median OS not yet reached [18]. In another trial, radiotherapy plus camrelizumab resulted in an ORR of 74%. At a median follow-up of 31.0 months (95% CI, 27.0–35.1), the median OS was 16.7 months (95% CI, 5.9–27.9), and the median PFS was 11.7 months (95% CI, 0–30.3) [26]. In addition, the safety profile of combined RT and ICIs (camrelizumab/toripalimab) aligns with those of the individual treatments [18, 26]. All patients encountered treatment-related adverse events (AEs), though the majority were mild to moderate (grade 1–2), with no grade 5 events observed. All the Grade 3 and 4 radiotherapy-related AEs, such as lymphopenia, esophagitis, laryngitis, and leukopenia could be managed without discontinuation of radiotherapy, which suggested that the combined therapy does not exacerbate radiotherapy-related toxicities and may even be less severe than those noted with cCRT [16, 17, 19]. The incidence of grade 3 pneumonitis was 5%, comparable to the 6.7% rate observed with camrelizumab alone [28].

Another novel aspect of this study is the integration of immunonutrition support to the immunoradiotherapy which may improve the efficacy. One of the major reasons for poor outcomes in ESCC patients is a profound malnutrition. Epidemiological surveys indicated around 57 – 69% of patients experience marked body weight reductions (about 13–16% loss) [31, 32], across inpatient and outpatient cohorts [33]. The malnutrition is exacerbated by a cytokine-mediated inflammatory state, which impairs the host's immune response and tissue regeneration and emerges as an autonomous risk determinant for complications associated with treatment [31, 34]. Pharmaconutrition, also referred to as immune-modulating nutrition (IMN) containing specific nutrients to improve nutritional condition while concurrently modulating the host's immunological response and its inflammatory reaction to stress, presenting a potential therapeutic avenue [35, 36]. For instance, studies by Kemen et al. and Sorensen et al. demonstrated that nutritional support enriched with omega-3 fatty acids, ribonucleic acids, and arginine increased T lymphocytes in gastrointestinal and head and neck cancer patients within 10 days [37, 38]. A randomized controlled trial with 71 esophageal cancer patients showed that IN, containing arginine, glutamine, and omega-3 fatty acids, maintained a lower CD4/CD8 ratio compared to a standard formula, suggesting better immune modulation [39]. Further findings involving 28 patients undergoing RT for esophageal and head and neck cancers, who received an IMN formula enriched with eicosapentaenoic and docosahexaenoic acids, arginine, and nucleotides, reported no decline in the CD4/CD8 ratio and reduced IFN-g production, indicating sustained immune function [40]. Our previous study systematically evaluated the combined effects of anti-PD-1 treatment and IMN on tumor growth and immune modulation in a xenograft tumor model in mice [41]. Our findings revealed that anti-PD-1 combined with IMN supplementation, significantly inhibited tumor growth more effectively than anti-PD-1 treatment alone. These results collectively suggest that IMN may help modulate immune responses and reduce inflammation during radiotherapy, potentially enhancing the host's capacity to manage oxidative stress and systemic inflammation.

In conclusion, the study protocol reflects a rigorous design that prioritizes safety and potential clinical benefit. The addition of immunonutrition is intended to support overall patient tolerance and potentially increase ICIs efficacy by modulating host-tumor immune reaction. Should the results confirm the hypothesis that the current combination therapy is both safer and effective, it could improve the current treatment paradigm for non-metastatic inoperable ESCC patients, offering a viable, less toxic treatment option without comprising efficacy.

Abbreviations

cCRT	Concurrent chemoradiotherapy
PD-1	Programmed cell death protein 1
ESCC	Esophageal squamous cell cancer
LA	locally advanced
ICIs	Immune checkpoint inhibitors
TPF-T	Enteral nutritional emulsion
TPS	Tumor proportion score
CPS	Combined positive score

ECOG	Eastern cooperative oncology group
NSCLC	Non-small cell lung cancer
CTCAE	Common terminology criteria for adverse events
RECIST	Response evaluation criteria in solid tumors
PFS	Progression-free survival
ORR	Objective response rate
AE	Adverse event
RT	Radiotherapy
IMN	Immune-modulating nutrition

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Author contributions
N.B. and J.D.; methodology, J.W. and F.H.; formal analysis, J.W., F.H. and L.W.; data curation, Y.M., Y.Y, Y.W and X.X; writing—original draft preparation, J.W. and F.H.; writing—review and editing, N.B., J.D. and L.W.; supervision and project administration, N.B. and J.D. All authors have read and agreed to the published version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study adheres to the ethical principles set forth in the Declaration of Helsinki and the International Ethical Guidelines of the Council for International Organizations of Medical Sciences. All participants will provide written informed consent prior to their inclusion in the study. Ethical approval has been granted by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital, affiliated with the Chinese Academy of Medical Sciences and Peking Union Medical College (Study ID: NCC4409). The study's protocol is registered on ClinicalTrials.gov under the identifier NCT06342167.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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