A phase II clinical trial of toripalimab combined with neoadjuvant chemoradiotherapy in locally advanced esophageal squamous cell carcinoma (NEOCRTEC1901)

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eClinicalMedicine 2023;62: 102118
Published Online xxx
https://doi.org/10.1016/j.eclinm.2023.102118

Summary

Background To evaluate the efficacy and safety of toripalimab combined with neoadjuvant chemoradiotherapy (NCRT) for locally advanced esophageal squamous cell carcinoma (ESCC).

Methods In this single arm, phase II trial, 44 ESCC patients were enrolled from December 2019 to July 2021 at Sun Yat-sen University Cancer Center (Guangzhou, China). All patients received concurrent radiotherapy (44 Gy in 20 fractions), chemotherapy (paclitaxel 50 mg/m^2 and cisplatin 25 mg/m^2 on days 1, 8, 15, and 22), and toripalimab (240 mg on days 1 and 22). Within 6–8 weeks of neoadjuvant treatment, patients underwent surgery. The results of the study patients were compared with those of 86 matched patients between July 2015 and March 2022. The primary endpoint was pathological complete response (pCR) rate, and the secondary endpoints were treatment-related adverse events and R0 rates. This trail was registered with ClinicalTrails.gov, NCT04006041.

Findings All patients received neoadjuvant treatment, and 42 completed esophagectomy. Of the 42 patients, 21 (50%; 95% CI 35–65) achieved pCR and 2 (5%) patients were ypT0N+. The R0 resection rate was 98% (41/42). Nine (20%) of 44 patients had grade 3/4 adverse events. Among the perioperative complications (n = 42), anastomotic leakage occurred in five cases (12%), tracheal fistula in three cases (7%), and postoperative death in one case (2%) due to tracheal fistula. Compared with the control cohort, the pCR rate of the study group was higher but without significant difference (50% vs. 36%, $P = 0.19$).

Interpretation Toripalimab combined with NCRT failed to show significantly better pCR rate than historical data. Nevertheless, considering the signs of efficacy and acceptable safety of this regimen, further evaluation in phase III randomized trials might be warranted.

Funding National Natural Science Foundation of China.

Keywords: Esophageal squamous cell carcinoma; Toripalimab; Neoadjuvant chemoradiotherapy; Pathological complete response; Safety

Introduction

Esophageal cancer (EC) is the seventh most common cancer worldwide.[1] In China, nearly 375,000 patients with EC die annually, and new cases and deaths account for more than half of those globally. Moreover, more than 90% of Chinese patients with EC have esophageal squamous cell carcinoma (ESCC).[2] Neoadjuvant chemoradiotherapy (NCRT) followed by surgery is the standard treatment for locally advanced EC.[3] However, over 40% of patients experience disease recurrence and

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Research in context

Evidence before this study

We searched PubMed, Embase, Cochrane Library and Web of Science for relevant publications until February 15, 2023, using the search terms ("esophageal squamous cell carcinoma" or "esophageal squamous cell cancer"), and ("neoadjuvant" or "preoperative"), and ("immunotherapy" or "immune checkpoint inhibitors" or "PD-1/PD-L1 blockades" or "anti-PD-1/PD-L1" or "pembrolizumab" or "nivolumab" or "atezolizumab" or "durvalumab" or "avelumab" or "camrelizumab" or "sintilimab" or "toripalimab" or "tislelizumab"), and ("chemoradiotherapy" OR "chemoradiation"). The search was limited to clinical trials, with no language restrictions. Abstracts of recent important meetings were also inspected, including the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), and American Society for Radiation Oncology (ASTRO). References of relevant studies were reviewed for additional articles. Our search yielded 6 studies, including 5 ongoing trials with study protocol and 1 trials with published results. The published trial is a phase Ib study which investigated the safety and feasibility of preoperative pembrolizumab combined with neoadjuvant chemoradiotherapy for esophageal squamous cell carcinoma in 20 patients.

Added value of this study

To our knowledge, our study is the first phase II trial reporting the efficacy and safety of anti-PD-1 antibody plus neoadjuvant chemoradiotherapy in locally advanced esophageal squamous cell carcinoma. Our results demonstrated that combining toripalimab with neoadjuvant chemoradiotherapy provided encouraging antitumor activity with a pathological complete response rate of 50% and an acceptable safety profile in esophageal squamous cell carcinoma.

Implications of all the available evidence

Our results combined with existing evidence might support anti-PD-1 antibody plus neoadjuvant chemoradiotherapy is an effective and tolerable treatment option for locally advanced esophageal squamous cell carcinoma. We believe that phase III randomized trials are warranted to validate the clinical benefits of this combination.

death within 5 years of this combined therapy.[4,5] Therefore, more effective strategies are required to improve the survival rates.

Immunotherapy, particularly with anti-programmed cell death-1 (PD-1) or anti-programmed cell death-ligand 1 (PD-L1) antibody, has remarkably improved survival outcomes for various tumor types.[6] For patients with advanced EC, anti-PD-1 antibody has demonstrated promising efficacy. Based on the substantial results of phase III trials,[7–9] anti-PD-1 therapy in combination with chemotherapy is recommended as the first-line treatment for recurrent and metastatic EC.[3,10] In the JUPITER-6 trial, toripalimab, a humanized IgG4 anti-PD-1 monoclonal antibody, plus chemotherapy significantly improves progression-free survival and overall survival (OS) compared with chemotherapy alone in advanced ESCC.[9]

The addition of PD-1/PD-L1 inhibitors to NCRT, which may have synergistic antitumor activity and achieve greater efficacy, has emerged as a novel approach for treating locally advanced EC.[11–14] Several studies have been conducted to investigate the efficacy and safety of neoadjuvant PD-1/PD-L1 inhibitors plus NCRT for patients with EC.[12–14] However, the results of these previous studies are inconsistent. Moreover, most studies were conducted in Western countries,[12,13] which only enrolled patients with esophageal or esophagogastric junction adenocarcinoma. Although the PALACE-1 phase IB trial included patients with ESCC, the sample size for efficacy evaluation was relatively small.[11] More data are needed to assess the effects of preoperative administration of PD-1 inhibitors combined with NCRT in patients with locally advanced ESCC. This phase II trial aimed to investigate the efficacy and safety of neoadjuvant toripalimab plus concurrent chemoradiotherapy (CRT) followed by surgery in patients with resectable locally advanced ESCC.

Methods

Ethics statement

The study protocol (Supplement) was approved by the Ethics Commission of Sun Yat-sen University Cancer Center (SL-B2019-038-05). Written informed consent was obtained from all the patients prior to participation in the study. This trial was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Study design and participants

This open-label, single-center, single-arm, phase II study was conducted at the Sun Yat-sen University Cancer Center (Guangzhou, China). From December 2019 to July 2021, 44 patients were enrolled in this study. Key eligibility criteria included previously untreated, histologically confirmed, potentially resectable thoracic ESCC clinically staged as T1-4aN1-3M0 or T3-4aN0M0 according to the 8th edition of the UICC staging system, age 18–70 years, normal hematologic and organ function, and Eastern Cooperative Oncology Group performance status of 0 or 1. The key exclusion criteria included a history of other malignancies,

previous antitumor therapy, severe comorbidities, active autoimmune disease, prior non-infectious pneumonitis, or interstitial lung disease. The complete inclusion and exclusion criteria are listed in the trial protocol (Appendix).

Pretreatment workup and staging

All patients underwent the following pretreatment workup and staging: physical examination, standard blood tests, neck/chest/abdominal computed tomography with contrast, esophagogastroduodenoscopy with endoscopic ultrasound, cervical ultrasonography, pulmonary function tests, and echocardiography. Positron emission tomography was recommended but not mandatory. If indicated, bronchoscopy or ultrasonic bronchoscopy was performed to exclude tumor invasion into the trachea or bronchus.

Procedures

Neoadjuvant radiotherapy was delivered with 6 MV equipment using intensity-modulated radiotherapy (IMRT). Gross tumor volume (GTV) was defined as the primary tumor and involved lymph nodes. Clinical target volume (CTV) was defined as the primary tumor plus 3-cm proximal and distal margins and a radial margin of 0.5–1.0 cm, as well as the nodal GTV plus an expansion of 0.5–1.0 cm. All patients received a simultaneous integrated boost of IMRT in 20 fractions, 5 days per week (40 Gy to the CTV and 44 Gy to the GTV). As part of the quality assurance for radiotherapy, all radiation plans were subjected to a centralized review to assess compliance with the protocol requirements before treatment.

The concurrent chemotherapy regimen consisted of four cycles of weekly intravenous paclitaxel (50 mg/m^2) and cisplatin (25 mg/m^2) during radiotherapy. Two cycles of toripalimab (240 mg) were administered intravenously on days 1 and 22 in combination with NCRT. Details of the dose adjustment for chemotherapy and quality assurance for radiotherapy are provided in the trial protocol (Appendix). All patients underwent restaging 4–6 weeks after the completion of NCRT to assess their surgical eligibility.

Surgery was performed within 6–8 weeks after the completion of neoadjuvant therapy. The patients underwent McKeown or Ivor Lewis esophagectomy with two-field lymph node dissection. A jejunal tube via the nose or jejunostomy tube was placed. Radical resection was defined as a macroscopic observation with negative postoperative pathological margins. No adjuvant treatment after esophagectomy was administered.

Adverse events (AEs) and laboratory test results were evaluated weekly during neoadjuvant treatment according to the Common Terminology Criteria for Adverse Events (version 4.0). The post-operative complications within 30 days after surgery were graded according to the Clavien-Dindo classification.[15] Post-treatment follow-up was performed every 3 months within the first year, every 3–6 months for the next 4 years, and annually thereafter.

Pathologic analysis

The resected specimens were macroscopically and microscopically reviewed by a team of experienced pathologists. Pathologic reports included the following: site, type, and histologic grade of the tumor, depth of invasion, resection margins, pathologic response according to the tumor regression grade (TRG) system,[16] lymph node site, node number, and response of lymph nodes. Pathological complete response (pCR) was defined as the absence of residual tumor within the esophagus and resected lymph nodes.

Outcomes

The primary endpoint was pCR rate, and the secondary endpoints were safety, R0 resection rate, perioperative morbidity and mortality rates, OS, and disease-free survival (DFS). The exploratory endpoint was the association between PD-L1 expression and treatment efficacy. OS and disease-free survival are not reported in this manuscript due to data immaturity.

Biomarker analysis

Baseline tumor biopsies were stored in formalin-fixed paraffin-embedded blocks. PD-L1 expression was evaluated using immunohistochemical staining with the 22C3 antibody (Dako, Glostrup, Denmark). PD-L1 expression was reported using the combined positive score (CPS) and tumor proportion score (TPS). CPS was defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells multiplied by 100. TPS was determined as the percentage of tumor cells with partial or complete staining relative to all tumor cells in the sample.

Matching comparison

This nonrandomized trial did not enroll patients who received conventional NCRT; thus, we compared the outcomes of our study patients with those of a cohort of similar patients with ESCC who received standard NCRT followed by esophagectomy at the same institution from July 2015 to March 2022, as an exploratory post-hoc analysis. All patients in the control cohort received concurrent taxane/cisplatin chemotherapy and neoadjuvant IMRT with similar prescription dose. Then propensity score matching was performed based on the following baseline variables to balance potential confounding factors: age, sex, performance status, tumor location, and TNM stage. A 1:2 matching ratio was used with a caliper of 0.1.

Statistical analysis

The sample size calculation was based on the primary endpoint of pCR rate after esophagectomy. Assuming that the pCR rate with NCRT in ESCC as the historical control was 35%,[5,17,18] the addition of toripalimab improved the pCR rate to 60%. Based on a two-sided alpha of 0.05 and a beta of 0.10, the total sample size was 40 patients. With a presumed dropout rate of 10%, 44 patients were enrolled in this study.

The cutoff date for data collection was April 01, 2023. All enrolled patients were included in safety analysis, while only patients who received esophagectomy were included in efficacy analysis. Age and tumor length were presented as medians and interquartile ranges (IQRs), and categorical variables were presented as frequencies and percentages. Mann–Whitney U-test was used to compare continuous variables and Fisher's exact test was performed for categorical variables. The *P*-value was reported as the two-tailed exact probability for tables with larger dimensions than 2 × 2 or as double the exact one-tailed probability for 2 × 2 tables. The Kaplan–Meier method was used to estimate OS, DFS, and the corresponding 95% CIs. Statistical significance was set at a two-sided *P*-value of <0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0; Armonk, NY, USA). The trial was registered at ClinicalTrials.gov (NCT04006041).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding authors (JF, MX, and HY) had full access to the dataset of the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

From December 2019 to July 2021, 61 patients were screened, and 44 patients with locally advanced ESCC were enrolled in this study (Fig. 1). The baseline patient characteristics are shown in Table 1. The median age of the participants was 60 years (IQR, 54–63 years), and the majority of primary tumors were located in the middle or distal third of the esophagus (42/44, 96%). Thirty (30/44, 68%) and nine (9/44, 20%) patients had stage III and IVA diseases, respectively.

Treatment compliance

With regard to neoadjuvant treatment, 43 of the 44 patients (98%) completed the planned radiation dose of 44 Gy, 42 (96%) completed all four planned cycles of chemotherapy, and 43 (98%) received two cycles of toripalimab. Details of treatment compliance are listed in Appendix Table S1. Forty-two patients (42/44, 96%) underwent surgery after NCRT. The reasons for cancellation of surgery were patient refusal (n = 1) and death due to esophageal hemorrhage (n = 1).

Efficacy

After neoadjuvant treatment, the overall response rate and disease control rate were 77% (34/44) and 98% (43/44), respectively. Forty-two patients underwent minimally invasive surgery, and the median interval between completion of NCRT and surgery was 51 days (IQR, 46–59 days). After pathologic evaluation of 42 patients, 21 patients (50%; 95% CI 35–65) achieved pCR, and 2 patients (5%) were ypT0N+. R0 resection was achieved in 41 patients (41/42, 98%), and the median number of resected lymph nodes was 31 (IQR, 24–35). The TRG scores were as follows: TRG 0 (23/42, 55%), TRG 1 (11/42, 26%), and TRG 2 (8/42, 19%; Fig. 2A).

With a median follow-up of 28.0 months (IQR, 24.8–31.5 months), 9 (20%) of 44 patients developed a relapse and 8 (18%) patients died. Details regarding the recurrence pattern and reasons for death are shown in Appendix Table S2. For the entire cohort, the 2-year OS rate was 81.5% (95% CI 67.1–93.4) and 2-year DFS rate was 79.2% (95% CI 70.7–94.0; Appendix Fig. S1).

Safety

During neoadjuvant treatment, 42 of the 44 patients (96%) experienced treatment-related AEs, and 9 patients (20%) experienced grade 3–4 AEs (Table 2). The most common AEs were radiation esophagitis (37/44, 84%), anemia (30/44, 68%), nausea/vomiting (28/44, 64%), anorexia (25/44, 57%), and leukopenia (25/44, 57%). The most common grade 3–4 AEs were leukopenia (4/44, 9%) and nausea/vomiting (2/44, 4%). One patient (1/44, 2%) developed a grade 5 esophageal hemorrhage after NCRT. No significant associations were observed between grade ≥3 treatment-related AEs and pCR rate ($P = 0.41$). In total, 14 of 44 patients (32%) experienced immune-related AEs, and the most common were rashes (11/44, 25%), fatigue (7/44, 16%), and hyperthyroidism (1/44, 2%). All the patients recovered without severe sequelae.

The postoperative complications are summarized in Table 3. Five patients (5/42, 12%) experienced grade ≥3 postoperative complications. The most common surgical complications were pulmonary complications (9/42, 21%), anastomotic leakage (5/42, 12%), and arrhythmia (5/42, 12%). None of the patients died within 30 days after surgery, but one patient (1/42, 2%) died of tracheal fistula within 90 days postoperatively.

PD-L1 expression

Baseline PD-L1 expression data were available for 41 patients, 39 of whom underwent surgery. Representative radiological and immunohistochemical images are shown in Fig. 2B. The pCR rate was slightly higher in patients with PD-L1 CPS ≥ 10 than in those with PD-L1 CPS < 10, but the difference was not statistically

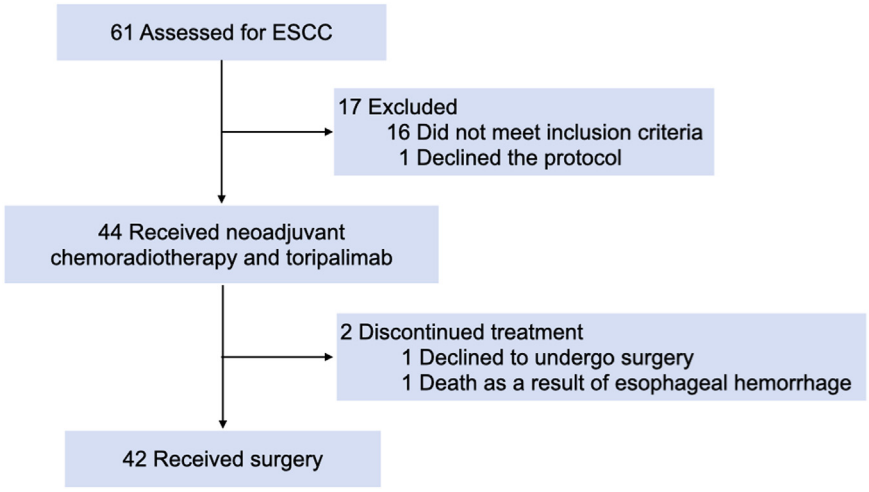

Fig. 1: CONSORT diagram of the trial.

significant (55% vs. 47%, $P = 0.88$; Fig. 2C). Similarly, no significant difference in pCR rates was observed in patients with PD-L1 CPS ≥ 1 versus in those with PD-L1 CPS < 1. We also compared the pCR rates and TRG scores between patients with different PD-L1 expression levels at cut-offs of 1% and 10% according to TPS (Fig. 2D and Appendix Fig. S2). However, none of the differences were statistically significant (Appendix Table S3).

Propensity score matching analysis

Of 170 patients who received standard NCRT followed by surgery between July 2015 to March 2022, 86 patients (control cohort) were matched with the 44 patients in the study group for exploratory post-hoc analysis (Appendix Table S4). With comparable baseline characteristics after matching, no significant differences were observed in treatment-related AEs during CRT between the two cohorts (Appendix Table S5). Moreover, the occurrence of surgical complications and R0 resection rate between the two cohorts were not significantly different (Appendix Table S6).

In terms of efficacy, 31 patients (36%) achieved pCR, and 4 patients (5%) achieved ypT0N+ in the control cohort of 86 patients. TRG 0 was recorded in 36 (42%) patients, TRG 1 in 30 (44%) patients, TRG 2 in 18 (21%) patients, and TRG 3 in 2 (2%) patients (Appendix Table S7). The study cohort showed a higher pCR rate than the control cohort; however, this difference was not statistically significant (50% vs. 36%, $P = 0.19$). The subgroup analyses based on matched confounding factors still demonstrated a higher rate of pCR in the study cohort, despite the lack of statistical significance in subgroups (Appendix Table S8). Moreover, the study cohort had a lower percentage of ypTxN + cases than the control cohort, but the difference was not statistically significant as well (17% vs. 28%, $P = 0.24$).

Discussion

This NEOCRTEC1901 phase II clinical trial provided evidence for the combination of anti-PD-1 antibody toripalimab and concurrent CRT as neoadjuvant therapy for locally advanced ESCC, which resulted in a pCR rate of 50% (95% CI 35–65) and a R0 resection rate of 98%. In addition, the neoadjuvant therapy regimen based on toripalimab, paclitaxel, and cisplatin had a favorable safety profile. Compared with those treated with NCRT plus surgery, patients treated with neoadjuvant immunotherapy plus CRT followed by surgery had similar postoperative complication and perioperative mortality rates.

Preoperative CRT plus surgery is the standard treatment for patients with locally advanced ESCC worldwide.[19,20] Based on previous studies investigating the therapeutic efficacy of preoperative CRT in patients with EC,[4,5,18,21–25] the pCR rates ranged from 25% to 43%. pCR after NCRT is an independent positive prognostic factor in EC.[18] In the current study, neoadjuvant toripalimab plus concurrent CRT resulted in a pCR rate of 50%, which was better than that reported in previous NCRT studies.[4,21–25] Several factors contributed to the pCR improvement in this combined therapy observed in the current study. First, by blocking the binding between PD-1 and its ligands to restore cytotoxic T-cell antitumor activity, immunotherapy targeting the PD-1/PD-L1 checkpoints has demonstrated promising activity against advanced EC.[26,27] Second, preclinical studies have shown that the combination of PD-1/PD-L1 inhibitors and chemotherapy or radiotherapy could have a synergistic antitumor effect.[28,29] In addition, radiotherapy can promote CD8+ T cell infiltration and upregulate PD-L1 expression in the tumor microenvironment, thus overcoming immunosuppression and improving the efficacy of immunotherapy.[30,31] Because patients with ESCC who achieve pCR benefit most from combined therapy,[32–35] neoadjuvant toripalimab plus concurrent CRT could

Characteristics	No. (%)
Age, years	
Median	60
IQR	54–63
Sex	
Male	34 (77)
Female	10 (23)
ECOG performance status	
0	21 (48)
1	23 (52)
BMI, kg/m2	
≥18.5	41 (93)
<18.5	3 (7)
Tumor length, cm	
Median	5.7
IQR	4.2–7.7
Tumor differentiation	
G1	1 (2)
G2	19 (43)
G3	12 (27)
Gx	12 (27)
Tumor location	
Proximal third	2 (4)
Middle third	21 (48)
Distal third	21 (48)
Clinical T stage	
T1b	2 (4)
T2	8 (18)
T3	32 (73)
T4a	2 (4)
Clinical N stage	
N0	2 (4)
N1	15 (34)
N2	20 (46)
N3	7 (16)
Clinical TNM stage	
I	1 (2)
II	4 (9)
III	30 (68)
IVA	9 (20)
PD-L1 expression	
CPS ≥ 10	20 (46)
CPS < 10	21 (48)
TPS ≥ 1%	19 (43)
TPS < 1%	22 (50)
Unknown	3 (7)

IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; PD-L1, programmed cell death-ligand 1; CPS, combined positivity score; TPS, tumor proportion score.

Table 1: **Baseline characteristics (N = 44).**

possibly prolong the OS of these patients by increasing the pCR rate.

Previous studies investigating the efficacy of neoadjuvant immunotherapy plus CRT in patients with EC reported conflicting results.[11–13] The PALACE-1 phase IB trial indicated that preoperative pembrolizumab with concurrent CRT can achieve a pCR rate of 55.6% (10/18) and is manageably safe for patients with resectable ESCC.[11] Nevertheless, the pCR rate of this combined model for ESCC is questionable because the sample size is relatively small. The PALACE-2 phase II study is ongoing to confirm its efficacy (NCT04435197). The PERFECT single-arm phase II clinical trial recruited 40 patients with resectable esophageal adenocarcinoma (EAC). The results showed that NCRT combined with PD-L1 inhibition (atezolizumab) induced a pCR rate of 30.3% (10/33).[12] Another phase IB/II study by Zhu et al. enrolled 31 patients with resectable adenocarcinoma of the gastroesophageal junction.[13] pCR was observed in 24.1% (7/29) of the patients who received preoperative pembrolizumab-containing chemoradiation. All the above studies employed the CROSS regimen (carboplatin and paclitaxel with concurrent 41.4 Gy radiotherapy). Several observational studies in East Asia investigating the outcome of the CROSS regimen have reported lower pCR rates of 28%–33% compared with western studies.[21–25] Eyck et al. conducted a propensity score matching study to compare the effectiveness of the CROSS regimen in different ethnic groups with ESCC. The pCR rate in the Asian group was significantly lower than that in the Dutch group (27.8% vs. 43.6%, $P = 0.010$).[36] The present study recruited 44 patients with ESCC and followed a different NCRT protocol (cisplatin and paclitaxel with concurrent 44 Gy radiotherapy). In our control cohort of patients treated with NCRT, a good response was observed, with a pCR rate of 36%. The addition of toripalimab to NCRT increased the pCR rate (50%) in our study, but the difference was not statistically significant between the two groups. Moreover, in the current study, patients with ypTxN + account for 16% (7/42), which was lower than NEOCRTEC5010 (33.0%).[37] Postsurgical pathological lymph node metastasis after NCRT is an independent poor prognostic factor in ESCC.[38] By increasing the pCR rate and reducing the ypN + rate, this combination therapy could hopefully improve the prognosis of patients with ESCC. With regard to toxicity, 9.1% of the patients in the study group developed grade 3 or higher leucopenia, and 95.5% of the patients completed the full treatment protocol with similar perioperative mortality rates as the NCRT group. Thus, safety and patient compliance were favorable.

Given that the CheckMate 648, KENOTE-590, and ESCORT-1st trials consistently demonstrated a positive association between the efficacy of PD-1 inhibitors plus chemotherapy and PD-L1 expression, PD-L1 status has emerged as a preferred biomarker in advanced EC.[7–9] To identify patients who may benefit from a combination of neoadjuvant immunotherapy and CRT, we investigated the predictive value of PD-L1 expression for tumor response. Nevertheless, our study did not show any

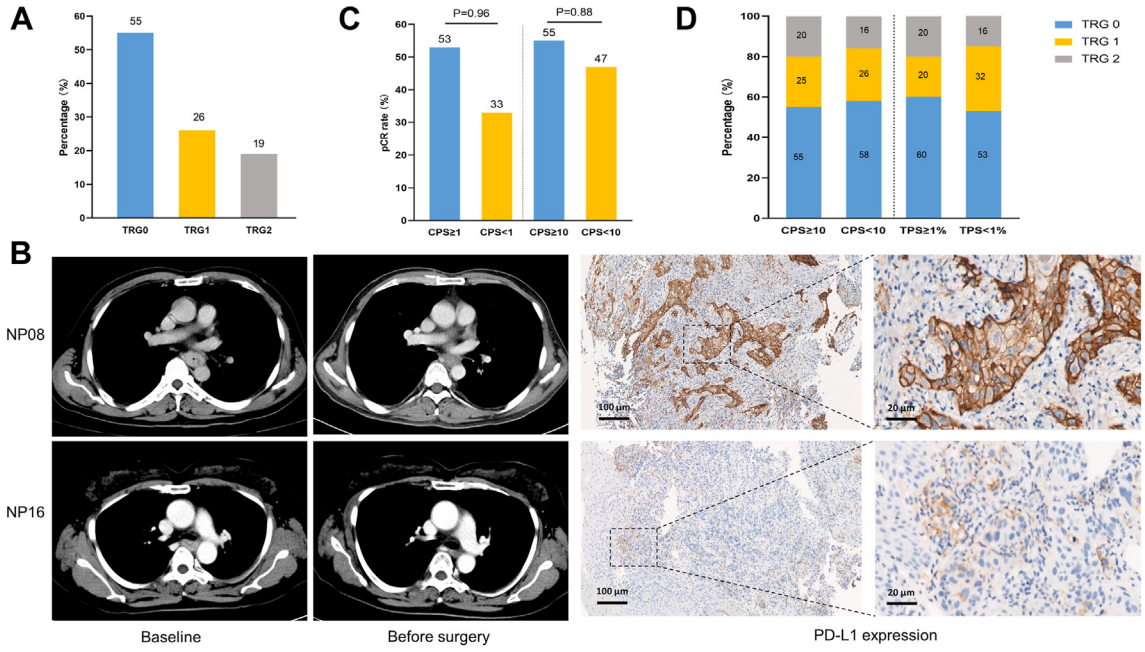

Fig. 2: Tumor response to neoadjuvant treatment. (A) TRG scores of the enrolled patients who proceeded to surgery (n = 42); (B) representative radiological and immunohistochemistry images of two patients who achieved pathological complete response with high or low PD-L1 expression; (C) relationship between pathological complete response rate and PD-L1 CPS; and (D) relationship between TRG score and PD-L1 expression.

correlation between PD-L1 expression and pCR rate. Consistent with our results, Li et al. failed to find any obvious relationship between PD-L1 expression and pathological regression in 20 patients with ESCC treated with neoadjuvant pembrolizumab and CRT.[11] By contrast, Zhu et al. recently reported that a PD-L1 CPS of

Adverse event	Grades 1-2	Grade 3	Grade 4	Grade 5
Radiation esophagitis	36 (82)	1 (2)	0	0
Anemia	29 (66)	0	1 (2)	0
Nausea/vomiting	26 (59)	2 (4)	0	0
Anorexia	25 (57)	0	0	0
Leukopenia	21 (48)	4 (9)	0	0
Weight loss	18 (41)	0	0	0
Dermatitis	17 (39)	0	0	0
Fatigue	12 (27)	0	0	0
Alopecia	12 (27)	0	0	0
Rash	11 (25)	0	0	0
Aminotransferase increased	10 (23)	0	0	0
Diarrhea	7 (16)	0	0	0
Constipation	5 (11)	0	0	0
Thrombocytopenia	4 (9)	1 (2)	0	0
Creatinine increased	3 (7)	0	0	0
Esophageal hemorrhage	1 (2)	0	0	1 (2)
Pneumonia	1 (2)	0	0	0
Arthralgia or myalgia	1 (2)	0	0	0
Hyperthyroidism	1 (2)	0	0	0
Arrhythmia	1 (2)	0	0	0

Table 2: **Treatment-related adverse events during neoadjuvant treatment (N = 44).**

Postoperative complications[a]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pulmonary infection	1 (2)	8 (19)	0	0	0
Anastomotic leakage	0	2 (5)	2 (5)	0	1 (2)
Atelectasis	3 (7)	0	0	0	0
Pneumothorax	3 (7)	0	0	0	0
Arrhythmia	1 (2)	4 (10)	0	0	0
Immune pneumonia	0 (0)	1 (2)	0	1 (2)	0
Abnormal liver function	0 (0)	2 (5)	0	0	0
Postoperative hemorrhage	0	0	1 (2)	0	0
Chylothorax	1 (2)	0	0	0	0
Heart failure	0	0	0	1 (2)	0
Anastomotic stenosis	1 (2)	0	0	0	0
Intestinal obstruction	0	1 (2)	0	0	0

[a]Complications were graded according to the Clavien-Dindo classification for surgical complications.

Table 3: **Postoperative complications (N = 42).**

≥10 is associated with a significantly higher pCR rate (50% vs. 13.6%, $P = 0.046$) and more favorable survival.[13] Similarly, in the phase II PERFECT trial, patients with EAC who had higher PD-L1 expression tend to have a higher pCR rate after NCRT combined with atezolizumab.[12] Taken together, these data suggest that the predictive value of PD-L1 status in patients with locally advanced EC is contradictory and not as strong as that in advanced settings. Moreover, the predictive role of PD-L1 may differ in patients with ESCC and patients with EAC.

The present trial has several limitations. First, this was a single-center study, which may have restricted the generalizability of the results. Second, this is a single-arm, phase II study with a small sample size, so a multi-center study with a large sample is needed to validate. Third, since our study lacked a control group, we set up historical controls. Certainly, we have the limitation that the historical controls might give misleading comparisons. Hence, prospective randomized controlled studies are still needed to further confirm our findings. Fourth, as reported by the JCOG1109 trial,[39] the increase of pCR rate did not affect long-term survival. Therefore, the long-term outcomes of this study needed to be followed up, and phase III randomized trials are also warranted. Fifth, the pCR rate was reported based on patients who underwent surgery after NCRT, but not based on the intent-to-treat patients in this study. Although this is a common method of analysis in esophageal cancer,[4,5] reporting a pCR rate with patients undergoing resection as the denominator might lead to overestimation of clinical efficacy. Finally, whether our results are applicable to western countries warrants further investigation. The following reasons might affect the promotion of our regimen in western countries: the pathological type of EC in Asia is mainly ESCC, while the major type is adenocarcinoma in western countries. On the other hand, the tumors in our study are mainly located in the thoracic esophagus, while the tumors are mainly in the gastroesophageal junction in western countries, which has an impact on risk of radiotherapy and surgery. In addition, we strictly adhered to performing two-field lymphadenectomy with total mediastinal lymph node dissection in ESCC at our institution, especially recurrent laryngeal nerve node dissection, which was not required in western countries.

In conclusion, toripalimab combined with NCRT failed to show significantly better pCR rate than historical data in ESCC. Nevertheless, considering the signs of efficacy and acceptable safety of this regimen, further evaluation in phase III randomized trials might be warranted.

Contributors

Conception and design: JF, MX, and HY.

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All authors had access to the data, participated in reviewing and editing of the manuscript, and approved the final version before submission. Three principal investigators (JF, MX, and HY) verified the raw data of the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Individual data will be made available following publication by reasonable request to the corresponding author. The study protocol is available in the appendix.

Declaration of interests

All authors have no conflicts of interest to declare.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 82272881) (No. 82273032) (No. 81972614) and Sci-Tech Project Foundation of Guangzhou (2022A1515012217). We thank all participating patients, investigators, research staff, and members of the Independent Data Monitoring Committee.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102118.

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