# Safety and efficacy of neoadjuvant toripalimab plus chemotherapy followed by chemoradiotherapy for locally advanced esophageal squamous cell carcinoma in China (GASTO 1071): a non-randomised, two-cohort, phase 2 trial

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## Summary

**Background** We aimed to explore the efficacy and safety of neoadjuvant toripalimab plus chemotherapy followed by concurrent chemoradiotherapy (CCRT) in locally advanced esophageal squamous cell carcinoma (ESCC).

**Methods** This phase II, non-randomized, 2-cohort study enrolled patients with unresectable, stage T1-4N0-3M0-1 ESCC (M1 only includes patients with lymph node metastasis in the supraclavicular region). Patients received neoadjuvant therapy comprised of albumin-bound paclitaxel, nedaplatin and toripalimab every 3 weeks, for 2 cycles, followed by CCRT (total dose 60Gy in cohort A, 50Gy in cohort B, combined with oral capecitabine). The primary endpoint was progression-free survival (PFS). The trial is registered with ClinicalTrials.gov, NCT04844385.

**Findings** Between February 26, 2021 and June 20, 2023, 124 patients were enrolled, and 118 (95.2%) patients completed treatment. The objective response rate to neoadjuvant chemo-immunotherapy was 91.9% overall, and was 93.7% in cohort A-60Gy and 93.4% in cohort B-50Gy after CCRT. With a median follow-up of 30.8 months, the 18-month PFS rates were 65.0% (95% CI, 53.9–78.3%) in cohort A-60Gy and 65.1% (95% CI, 53.7–78.8%) in cohort B-50Gy. Grade (G) 3 and G5 pneumonitis occurred in two (3.2%) and one patient (1.6%) in cohort A-60Gy, respectively, with no ≥G3 pneumonitis in cohort B-50Gy. Improvements on patient reported outcomes from baseline to 12 months post-CCRT were observed overall.

**Interpretation** Neoadjuvant chemo-immunotherapy, radiotherapy and concurrent capecitabine achieved promising efficacy in locally advanced ESCC. Further investigation is warranted.

**Funding** None.



*Abbreviations:* CCRT, concurrent chemoradiotherapy; CIs, confidence intervals; CPS, combined positive score; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTV, clinical target volume; DMFS, distant metastasis-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Core 30; ESCC, esophageal squamous cell carcinoma; GTV, gross tumor volume; LRFS, locoregional recurrence-free survival; MMRM, mixed model for repeated measures; ORR, objective response rate; ORs, Odds ratios; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; PROs, patient-reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors

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## Research in context

### Evidence before this study

We searched PubMed for reports published in English until November 13th, 2024, with the search terms ("locally advanced esophageal squamous cell carcinoma" or "locally advanced esophageal squamous cell cancer" or "locally advanced esophageal cancer"), AND ("immune checkpoint inhibitors" or "PD-L1" or "PD-1"), AND ("induction" or "neoadjuvant") AND ("chemoradiotherapy" or "chemoradiation"). The search was limited to clinical trials. Our search yielded 1 prospective study for unresectable locally advanced esophageal cancer. The published single-arm, phase 2 trial, investigated the efficacy and safety of induction immunotherapy followed by concurrent chemoradiotherapy (CCRT) in 75 patients with locally advanced esophageal cancer. The findings revealed that combining induction immunotherapy with CCRT led to promising local control and progression-free survival.

### Added value of this study

Our phase II, non-randomized study designed two cohorts with radiotherapy doses of 60Gy and 50Gy respectively combined with concurrent capecitabine following neoadjuvant chemo-immunotherapy. The two cohorts achieved similar 18-month progression-free survival rates with 65.0% in cohort A-60Gy, and 65.1% in cohort B-50Gy. Furthermore, patients received radiotherapy of 50Gy might have better patient-reported outcomes without compromising treatment effectiveness. Our study supported the use of neoadjuvant chemo-immunotherapy before CCRT, and implied that a substantial response to neoadjuvant chemo-immunotherapy may allow for a reduction in the treatment intensity of subsequent CCRT.

### Implications of all the available evidence

Our results, when combined with existing evidence, support the addition of neoadjuvant chemo-immunotherapy to CCRT. Neoadjuvant chemo-immunotherapy, followed by radiotherapy and oral capecitabine, might be able to balance the efficacy and treatment related toxicities. Phase 3 randomized trials are warranted to further investigate the clinical benefits of this combination.

## Introduction

Esophageal cancer ranked as the seventh most prevalent malignancy and the sixth leading cause of cancer-related mortality worldwide in 2020.[1] Esophageal squamous cell carcinoma (ESCC) represents the predominant histological subtype in Asia, with over 320,000 new cases reported in China in 2020.[2] Concurrent chemoradiotherapy (CCRT) remains the standard treatment for unresectable locally advanced ESCC.[3] However, previous studies involving high-dose radiotherapy combined with cisplatin and fluorouracil have demonstrated increased toxicity and poor therapy compliance rates.[4,5] Moreover, more than 50% of patients develop locoregional or distant recurrences following definitive CCRT,[6,7] with 1-year progression-free survival (PFS) rates ranging from 40% to 66%.[4,8,9] Therefore, more effective and less toxic treatment strategies are urgently needed for this patient population.

A multicenter, randomized phase 3 trial assessed the efficacy and safety of capecitabine vs. fluorouracil plus cisplatin in definitive CCRT for locally advanced ESCC. The study found that concurrent capecitabine was associated with a lower incidence of ≥ grade (G)3 adverse events while maintaining comparable survival outcomes.[10] Our previous clinical trials have also shown that radiotherapy combined with capecitabine yields favorable survival outcomes with manageable treatment-related toxicities in patients with unresectable ESCC.[11,12] Additionally, the impact of radiation dose reduction using modern radiation techniques on locoregional control and survival outcomes have been investigated. The ARTDECO trial compared 61.6Gy with 50.4Gy in patients with medically inoperable and/or unresectable esophageal cancer, including both squamous cell carcinoma and adenocarcinoma, but did not find a significant improvement in PFS across histologic types.[8] Similarly, a Chinese randomized trial comparing 60Gy to 50Gy in locally advanced ESCC also failed to demonstrate an improvement in local/regional control and overall survival (OS).[13] These findings underscore the importance of reducing treatment toxicities to enhance long-term outcomes in ESCC patients.

Recently, the utilization of PD-1 inhibitors in combination with chemotherapy as neoadjuvant therapy has shown promising antitumor efficacy in resectable ESCC, achieving a pathological complete response rate of 20%–40%.[14–17] The application of chemo-immunotherapy before CCRT in unresectable locally advanced ESCC also offers several advantages. Firstly, chemo-immunotherapy can shrink the tumor prior to CCRT, rending it more susceptible to radiation therapy. Secondly, tumor shrinkage would alleviate tumor-related symptoms, thereby improving nutritional status and reducing the toxicity associated with subsequent CCRT.[18] Despite these potential benefits, the efficacy of neoadjuvant chemo-immunotherapy followed by CCRT

remains to be validated in patients with unresectable locally advanced ESCC.

Therefore, we hypothesize that a robust response to neoadjuvant chemo-immunotherapy could allow for a reduction in the treatment intensity of subsequent CCRT. The regimen of neoadjuvant chemo-immunotherapy, followed by radiotherapy and oral capecitabine, may effectively balance the efficacy and treatment related toxicities, which is crucial for patients with unresectable locally advanced ESCC. We designed this phase II, non-randomized study to evaluate the efficacy and safety of neoadjuvant toripalimab plus chemotherapy, followed by radiotherapy and concurrent capecitabine, in patients with locally advanced ESCC. A two-cohort design was employed to assess the efficacy of the radiation doses of 60Gy and 50Gy following neoadjuvant therapy, respectively.

## Methods

### Study design and participants

GASTO 1071 was a phase II, non-randomized, two-cohort study conducted at Sun Yat-sen University Cancer Center (Guangzhou, China). The eligibility criteria included patients with unresectable, stage T1-4N0-3M0-1 ESCC (M1 status was restricted to those with lymph node metastasis in the supraclavicular region); aged 18–80 years with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; no prior chemotherapy, radiotherapy, surgery, targeted therapy, or immunotherapy; an estimated life expectancy of at least 12 weeks; and adequate organ and bone marrow function. Patients were excluded if they had any of the following: a history of another malignancy; concurrent participation in another interventional clinical trial; prior immunotherapy; active autoimmune disease; a history of primary immunodeficiency disease; history of organ transplantation requiring immunosuppressive therapy; use of immunosuppressive drugs within 28 days prior to the first dose of study drug; major surgery within 4 weeks prior to enrollment; severe comorbidities such as active infection or congestive heart failure; or pregnant or breastfeeding females. The trial is registered with ClinicalTrials.gov, NCT04844385.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This study was approved by the institutional review board of Sun Yat-sen university cancer center. Written informed consent for the use and publication of clinical data was obtained from all patients.

### Treatments

Pre-treatment evaluation included a comprehensive physical examination, standard blood tests, ultrasound esophagogastroduodenoscopy, barium esophagogram, contrast-enhanced CT, bone scan and/or positron emission tomography (PET) scan, pulmonary function test, electrocardiogram, and echocardiography. Bronchoscopy was required if the tumor was suspected to invade the trachea or bronchus based on CT or endoscopic ultrasound findings.

All patients in two cohorts received neoadjuvant therapy consisting of albumin-bound paclitaxel (260 mg/m$^2$), nedaplatin (75 mg/m$^2$), and toripalimab (240 mg) on Day 1 of each 3-week cycle for a total of 2 cycles. Following neoadjuvant therapy, intensity-modulated radiotherapy was delivered 5 consecutive days per week using 6–8 MV X-ray, with a cumulative dose of 60Gy in 24 fractions for cohort A and 50Gy in 20 fractions for cohort B. Four-dimensional CT was utilized to account for respiratory motion. Gross tumor volume (GTV) was defined as visible primary tumors and positive lymph nodes identified through endoscopy, CT and/or PET scans. Clinical target volume (CTV) encompassed the primary GTV with an additional lateral margin of 0.5–1.0 cm, a longitudinal margin of 3.0 cm; the nodal GTV plus a lateral margin of 0.5 cm, a longitudinal margin of 1.0 cm, and also included elective lymph node regions. The elective lymph node regions included the predefined high-risk areas based on the location of the primary tumor. For cervical, upper, middle, and lower thoracic ESCC, the corresponding lymph node stations were 1/2/4, 1/2/4/7, 2/4/7/8/9, and 7/8/9/16/17, respectively. The planning target volume (PTV) encompassed the gross GTV and CTV with an isotropic margin of 5 mm. Dose constraints for organs at risk were specified as follows: mean lung dose less than 20Gy; the percentage of the total lung volume receiving ≥20Gy (lung $V_{20}$) less than 30%; the percentage of the total heart volume receiving ≥30Gy (heart $V_{30}$) less than 30%; the maximum spinal cord dose ≤45Gy. Capecitabine (1000 mg/m$^2$, bid) was administered orally on days 1–14 of each 3-week cycle during radiotherapy. Routine nutritional support commenced at the start of neoadjuvant therapy, including oral nutritional supplements, enteral nutrition via nasogastric tube or percutaneous endoscopic gastrostomy, and/or parenteral nutrition.

### Treatment response evaluation

Tumor assessments were conducted at baseline, 2 weeks post-neoadjuvant therapy, 2 months after definitive CCRT, and subsequently every 3–4 months for the first 2 years, every 6 months from years 3–5, and annually thereafter until disease progression, withdrawal of consent, initiation of new anti-cancer therapy, or death, whichever occurred first. Clinical response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1)[19] by two experienced radiologists using CT, and endoscopy. For patients with suspected recurrent disease after CCRT, PET was recommended. For patients with recurrent early-stage cancer, endoscopic ultrasonography was performed to evaluate the feasibility of endoscopic treatment. A complete response (CR) was defined as

fulfilling all of the following criteria: no lesion, budding, or ulceration identified by endoscopy; negative biopsy in case of suspicious endoscopic lesion; and the disappearance of all tumors and pathologic lymph nodes on CT (esophageal wall thickness <10 mm and lymph nodes with a short axis <10 mm were considered non-pathological on CT). In cases of ambiguous findings, a re-evaluation was performed within 4 weeks to determine the final response.

### Assessments of toxicity and patient-reported outcomes

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0) from the initiation of neoadjuvant therapy until 2 months after CCRT. Specifically, tracheal/esophageal fistula, esophageal stenosis, and pneumonitis were monitored from the start of treatment until one year after CCRT, or the initiation of new antitumor therapy, whichever came first. The severest observable toxicities were documented.

Patient-reported outcomes (PROs) were assessed using paper-based questionnaires at baseline, 2 weeks after neoadjuvant therapy, 2 months after CCRT, and 12 months after CCRT. We evaluated PRO symptoms, functioning, and global health status with two questionnaires: the European Organization for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30) and QLQ esophageal cancer 18 (QLQ-OES18), a disease specific module for esophageal cancer. All scales and single-item measures range in score from 0 to 100. A high score for the global health status and a functional scale of the QLQ-C30 indicates a good condition, while a high score for a constitutional cancer symptom scale of the QLQ-C30 and an esophageal cancer–specific symptom scale of the QLQ-OES18 represents worse condition. The longitudinal PRO scales of interest included global health status, function (physical function and emotional function), key symptoms (fatigue and appetite loss [QLQ-C30]; dysphagia, pain, and choking [QLQ-OES18]). Only questionnaires completed before disease progression were included in the analysis. Compliance at each time point was calculated using the number of patients who were alive and progression-free as the denominator.

### Treatment outcomes

The primary endpoint of the study was the 18-month PFS rate, assessed by investigators in the all enrolled patients. Secondary endpoints included OS, objective response rate (ORR), locoregional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), PROs and toxicity. PFS was defined as the duration from enrollment to disease progression, death from any cause, or censored at the last follow-up. OS was defined as the time from enrollment to death or censored at the last follow-up. ORR was defined as the proportion of patients with confirmed CR or partial response (PR). LRFS was defined as the time from enrollment to local or regional recurrence or date of death from any cause. DMFS was defined as the time from enrollment to the occurrence of distant metastasis or death from any cause.

### Statistical analysis

Based on a one-sided type-1 error rate of 0.05 and a power of 80%, it was estimated that the anticipated 18-month PFS rate following neoadjuvant toripalimab plus chemotherapy and definitive CCRT would be 65%, compared to a reference PFS rate of 50% in patients treated with CCRT,[20] assuming an accrual time of 24 months and a minimum follow-up time of 18 months. To achieve this, a total sample size of 52 patients in each cohort was calculated. Accounting for an estimated 10% dropout rate, the final sample size was determined to be 58 patients in each cohort.

Efficacy was assessed in all enrolled patients, and safety analyses were assessed in all patients who received at least one cycle of neoadjuvant therapy. Data collection was cut off on May 31, 2024. Follow-up duration was calculated from the date of enrollment to the date of the last follow-up. The Kaplan–Meier method was utilized to estimate PFS, OS, LRFS, DMFS, and their corresponding 95% confidence intervals (CIs) were calculated using the log–log transformation method. The Wilson score method was used to estimate the 95% CIs for ORR. The relationship between PD-L1 combined positive score (CPS) and the CR rate was analyzed using Pearson's chi-square test or continuity-corrected chi-square test. The Cox proportional hazards regression model was applied to calculate the hazard ratios (HRs) and their corresponding 95% CIs.

The analysis of PROs was a prespecified secondary endpoint. We assessed changes in global health status, function, and key symptoms from baseline to 12 months post-CCRT at each visit using a mixed model for repeated measures (MMRM) analysis. This model, which accommodates the collection of PROs across multiple visits and accounts for missing data, included fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as baseline score and baseline score-by-visit interaction. The patient was treated as a random-effect term, and the covariance structure was assumed to follow compound symmetry.

Any P-value $\leq 0.05$ was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) software version 26, GraphPad Prism (version 8.0.2), and R software (version 4.4.1).

### Role of the funding source

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

## Results

### Characteristics of patients and treatment dispositions

Between February 26, 2021, and June 20, 2023, a total of 63 patients were enrolled in cohort A-60Gy and 61 patients were enrolled in cohort B-50Gy (Fig. 1). In cohort A-60Gy, the mean age was 62 years (standard deviation [SD], 6). The majority were men (54/63, 85.7%) and smokers (38/63, 60.3%). Most patients (57/63, 90.5%) had stage III to IVB disease. In cohort B-50Gy, the median age was 64 years (SD, 8). There were 43 (70.5%) men and 37 (60.7%) smokers. Fifty-two (85.2%) patients had stage III to IVB disease (Table 1). Overall, 99 tumor samples were evaluable for PD-L1 expression, with 16 (25.4%) patients in cohort A-60Gy and 13 (21.3%) patients in cohort B-50Gy having PD-L1 CPS higher than 10. Specifically, there were 61 (96.8%) patients in cohort A-60Gy and 14 (23.0%) in cohort B-50Gy who received percutaneous gastrostomy for nutritional intervention. Patients in two cohorts shared similar baseline characteristics. The characteristics of the patients at baseline were potential representativeness of the ESCC population (Supplementary Table S1).

As of May 31, 2024, the data cutoff date, all patients (63 patients in cohort A-60Gy and 61 patients in cohort B-50Gy) received at least one dose of protocol-specified treatment and were included in the efficacy and safety analysis sets. There were 61 (96.8%) patients in cohort A-60Gy and 60 (98.4%) patients in cohort B-50Gy who completed neoadjuvant therapy. Three patients discontinued treatment due to: 1 (1.6%) patient had pneumonitis and 1 (1.6%) patient had immune-related hepatitis in cohort A-60Gy, while 1 (1.6%) patient had neuropathy in cohort B-50Gy. There were 60 (95.2%) patients in cohort A-60Gy and 61 (100%) patients in cohort B-50Gy who completed definitive CCRT. Three (4.8%) patients in cohort A-60Gy discontinued CCRT because of adverse events: 2 (3.2%) patients had pneumonitis and 1 (1.6%) patient had esophagitis (Table 2). The details of dosimetric parameters of patients in two cohorts are demonstrated in Supplementary Table S2.

### Anti-tumor response

All patients in two cohorts were evaluable for clinical response (Supplementary Table S3). The ORR to neoadjuvant chemo-immunotherapy was 90.5% (95% CI,

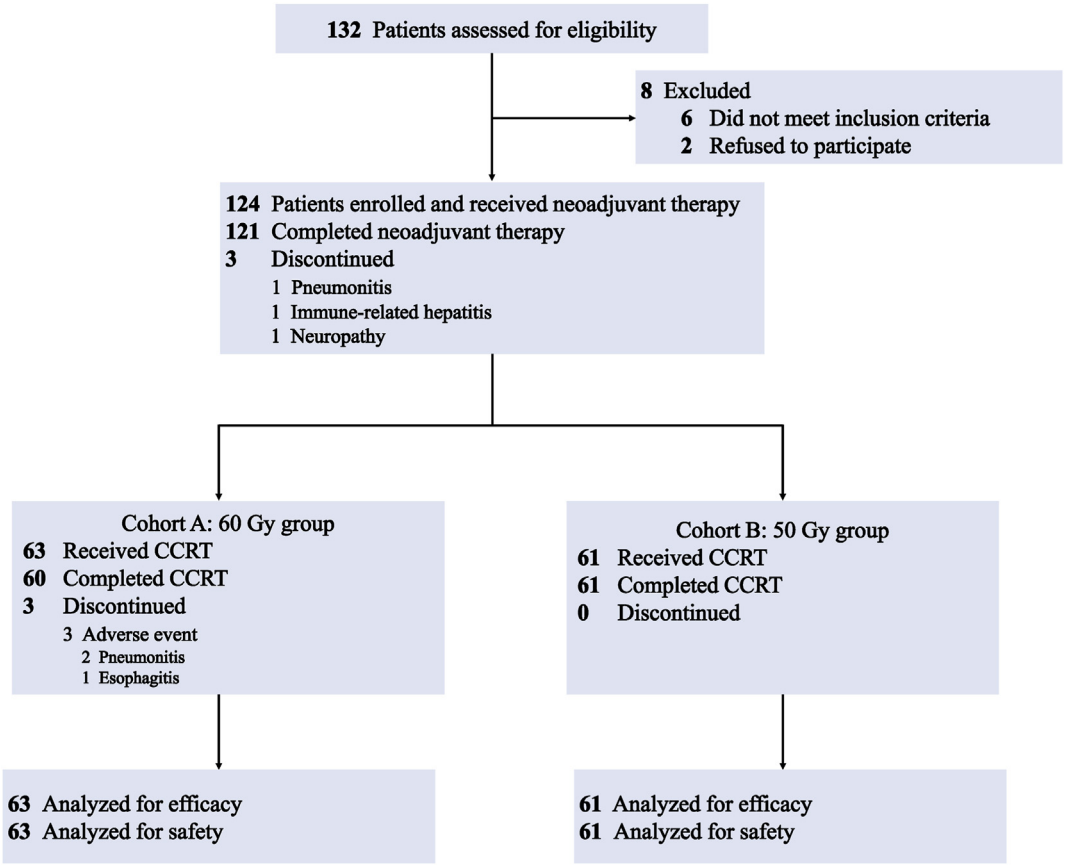


*Fig. 1:* Trial profile.

| Characteristic | Cohort A-60Gy (N = 63) | Cohort B-50Gy (N = 61) |
|---|---|---|
| Age, mean (yr, SD) | 62 (6) | 64 (8) |
| Sex | | |
| Female | 9 (14.3) | 18 (29.5) |
| Male | 54 (85.7) | 43 (70.5) |
| ECOG PS | | |
| 0 | 40 (63.5) | 44 (72.1) |
| 1 | 23 (36.5) | 17 (27.9) |
| Smoking history | | |
| Yes | 38 (60.3) | 37 (60.7) |
| No | 25 (39.7) | 24 (39.3) |
| Alcohol history | | |
| Yes | 28 (44.4) | 24 (39.3) |
| No | 35 (55.6) | 37 (60.7) |
| Family history of cancer | | |
| Yes | 3 (4.8) | 10 (16.4) |
| No | 60 (95.2) | 51 (83.6) |
| Bodyweight loss within 3 months | | |
| <10% | 54 (85.7) | 53 (86.9) |
| ≥10% | 9 (14.3) | 8 (13.1) |
| BMI, mean (kg/m$^2$, SD) | 21.9 (2.5) | 22.1 (2.9) |
| Primary tumor length | | |
| Median (cm, IQR) | 5.5 (3.9–7.2) | 5.0 (3.9–6.4) |
| <5 cm | 22 (34.9) | 30 (49.2) |
| ≥5 cm | 41 (65.1) | 31 (50.8) |
| Tumor location | | |
| Cervical | 5 (7.9) | 6 (9.8) |
| Upper | 18 (28.6) | 17 (27.9) |
| Middle | 22 (34.9) | 23 (37.7) |
| Distal | 18 (28.6) | 15 (24.6) |
| Clinical T stage | | |
| T1 | 3 (4.8) | 6 (9.8) |
| T2 | 8 (12.7) | 9 (14.8) |
| T3 | 31 (49.2) | 36 (59.0) |
| T4 | 21 (33.3) | 10 (16.4) |
| Clinical N stage | | |
| N0 | 3 (4.8) | 6 (9.8) |
| N1 | 13 (20.6) | 13 (21.3) |
| N2 | 23 (36.5) | 27 (44.3) |
| N3 | 24 (38.1) | 15 (24.6) |
| Clinical TNM stage | | |
| I–II | 6 (9.6) | 9 (14.8) |
| III | 19 (30.2) | 28 (45.8) |
| IVA | 22 (34.8) | 10 (16.4) |
| IVB | 16 (25.4) | 14 (23.0) |
| Reasons for no surgery | | |
| Technically unresectable | 55 (87.3) | 54 (88.5) |
| Patient refusal | 2 (3.2) | 3 (4.9) |
| Surgical contraindication | 6 (9.5) | 4 (6.6) |
| Dysphagia score | | |
| Able to eat normal diet | 9 (14.3) | 8 (13.1) |
| Able to swallow some solid foods | 23 (36.5) | 20 (32.8) |
| Able to swallow only semisolid foods | 22 (34.9) | 25 (41.0) |
| Able to swallow liquids only | 7 (11.1) | 5 (8.2) |
| Total dysphagia | 2 (3.2) | 3 (4.9) |
| PD-L1 expression[a] | | |
| CPS < 10 | 36 (57.1) | 34 (55.7) |
| CPS ≥ 10 | 16 (25.4) | 13 (21.3) |
| Unknown | 11 (17.5) | 14 (23.0) |

(Table 1 continued on next column)

(Continued from previous column)

Data are n (%) unless otherwise specified. BMI, body mass index; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SD, standard deviation. [a]Assessment of baseline PD-L1 expression was not mandatory for study enrollment. PD-L1 status was evaluated using immunohistochemistry staining with the 22C3 assay. PD-L1 expression was quantified as a CPS, calculated by dividing the number of PD-L1-positive cells (including tumor cells, lymphocytes, and macrophages) by the total number of viable tumor cells, and multiplying by 100. A CPS of 10 was determined as the cutoff point for analysis.

***Table 1:*** **Baseline characteristics for all patients.**

80.7–95.6%) in cohort A-60Gy (CR, 5/63, 8.0%; PR, 52/63, 82.5%), and 93.4% (95% CI, 84.3–97.4%) in cohort B-50Gy (CR, 10/61, 16.4%; PR, 47/61, 77.0%).

The overall ORR after CCRT was 93.7% (95% CI, 84.8–97.5%) in cohort A-60Gy (CR, 51/63, 81%; PR, 8/63, 12.7%), and 93.4% (95% CI, 84.3–97.4%) in cohort B-50Gy (CR, 41/61, 67.2%; PR, 16/61, 26.2%) (Fig. 2). Supplementary Fig. S1 demonstrated a typical case of anti-tumor response through treatment and follow-up.

## Survival outcome

By the data cutoff date of May 31, 2024, the median (IQR) follow-up duration was 40.0 (31.6–44.1) months in cohort A-60Gy, and 21.5 (16.3–27.4) months in cohort B-50Gy. There were 24 PFS events in cohort A-60Gy and 23 PFS events in cohort B-60Gy. A total of 39 patients (61.9%) in cohort A-60Gy were censored in the PFS analysis, either due to loss to follow-up (n = 5), or being alive at the last follow-up without experiencing progression (n = 34); 38 patients (62.3%) in cohort B-50Gy were censored due to loss to follow-up (n = 5), or being alive at the last follow-up without experiencing progression (n = 33). The 12-month PFS rates were 78.6% (95% CI, 69.0–89.7%) in cohort A-60Gy and 74.7% (95% CI, 64.3–86.6%) in cohort B-50Gy. The 18-month PFS rates were 65.0% (95% CI, 53.9–78.3%, one-sided $P < 0.0001$, compared with the historical control rate) in the cohort A-60Gy and 65.1% (95% CI, 53.7–78.8%, one-sided $P = 0.0003$, compared with the historical control rate) in the cohort B-50Gy (Fig. 3A and B). After excluding patients with loss of follow-up, the 18-month PFS rates were 63.8% (95% CI, 52.6–77.4%) in cohort A and 63.2% (95% CI, 51.5–77.6%) in cohort B (Supplementary Fig. S2). Median PFS was not reached in either cohort.

| Neoadjuvant therapy disposition | Cohort A-60Gy (N = 63) | Cohort B-50Gy (N = 61) |
|---|---|---|
| Patients who completed neoadjuvant therapy, n (%) | 61 (96.8) | 60 (98.4) |
| Patients who discontinued neoadjuvant therapy, n (%) | 2 (3.2) | 1 (1.6) |
| Pneumonitis | 1 (1.6) | 0 |
| Immune-related hepatitis | 1 (1.6) | 0 |
| Neuropathy | 0 | 1 (1.6) |
| **CCRT disposition** | | |
| Patients who completed CCRT, n (%) | 60 (95.2) | 61 (100) |
| Patients who discontinued CCRT, n (%) | 3 (4.8) | 0 |
| Adverse event | 3 (4.8) | 0 |
| Pneumonitis | 2 (3.2) | 0 |
| Esophagitis | 1 (1.6) | 0 |

CCRT, concurrent chemoradiotherapy.

*Table 2:* **Key patient disposition of two cohorts.**

Twenty-eight deaths were reported including 16 (25.4%) in cohort A-60Gy and 12 (19.7%) in cohort B-50Gy. A total of 47 patients (74.6%) in cohort A-60Gy were censored in the OS analysis for reasons including loss to follow-up (n = 6), and alive at the last follow-up (n = 41); 49 patients (80.3%) in cohort B-50Gy were censored due to loss to follow-up (n = 5), or alive at the last follow-up (n = 44). The 12-month and 18-month OS rates were 88.5% (95% CI, 80.9–96.9%), 85.0% (95% CI, 76.4–94.6%) in cohort A-60Gy, and 86.4% (95% CI, 78.0–95.6%), 82.5% (95% CI, 73.1–93.0%) in cohort B-50Gy. Median OS was not reached in either cohort (Supplementary Fig. S3).

### Patterns of disease progression

By the data cutoff date, 28.6% (18/63) and 27.8% (17/61) of patients had disease progression in cohort A-60Gy and cohort B-50Gy, respectively. Locoregional only progression occurred in 14.3% (9/63) and 24.6% (15/61); distant only progression in 11.1% (7/63) and 1.6% (1/61); and simultaneous locoregional/distant progression in 3.2% (2/63) and 1.6% (1/61), respectively. The 12-month and 18-month LRFS rates were 80.3% (95% CI, 70.8–90.9%), 70.0% (95% CI, 59.3–82.7%) in cohort A-60Gy, and 76.4% (95% CI, 66.3–88.0%), 66.8% (95% CI, 55.5–80.3%) in cohort B-50Gy (Supplementary Fig. S4). The 12-month and 18-month DMFS rates were 85.1% (95% CI, 76.5–94.6%), 78.1% (95% CI, 68.2–89.4%) in cohort A-60Gy, and 84.8% (95% CI, 76.1–94.5%), 80.8% (95% CI, 71.2–91.8%) in cohort B-50Gy (Supplementary Fig. S5). The most common site at progression was the esophagus in both cohorts (8 in cohort A and 15 in cohort B). Details about the recurrence pattern, recurrence sites and salvage treatments are provided in Supplementary Table S4.

### Treatment toxicity

All patients had treatment-related adverse events of any grade (Table 3). G3 or higher adverse events occurred in 59 (93.6%) patients in cohort A-60Gy and 49 (80.3%) patients in cohort B-50Gy. Treatment-related death occurred in 1 patient (1.6%) in cohort A-60Gy due to pneumonitis. The most common G3 or higher treatment-related adverse event was lymphopenia in both cohort A-60Gy (92.0%) and cohort B-50Gy (78.7%). G3 and G5 pneumonitis occurred in 2 (3.2%) and 1 patient (1.6%) in cohort A-60Gy, respectively, while no ≥G3 pneumonitis occurred in cohort B-50Gy. G3 esophagitis occurred in 10 (15.9%) and 5 (8.2%) patients in cohort A-60Gy and cohort B-50Gy, respectively. Treatment-related esophageal fistula occurred in 1 patient (1.6%) in both cohorts.

G2 or higher immune-related adverse events occurred in 9 (14.3%) patients in cohort A-60Gy and 8 (13.1%) patients in cohort B-50Gy, including G2 hypothyroidism (cohort A-60Gy, 2 [3.2%]; cohort B-50Gy, 3 [4.9%]), G2 rash (cohort A-60Gy, 4 [6.4%]; cohort B-50Gy, 1 [1.6%]), G2 hypertriglyceridaemia (cohort A-60Gy, 1 [1.6%]; cohort B-50Gy, 4 [6.6%]), G3 and G4 immuno-related hepatitis (cohort A-60Gy, 2 [3.2%]).

### Patient-reported outcomes (PROs)

All patients in both groups completed questionnaires at baseline and 2 weeks after neoadjuvant therapy. At 2 months post-CCRT, 98.4% of patients in cohort A-60Gy (61/62) and 96.7% of patients in cohort B-50Gy (58/60) completed the questionnaires. At 12 months post-CCRT, the completion rates were 91.8% (45/49) and 95.6% (43/45), respectively. Detailed results of the PRO analysis at each time point are summarized in Supplementary Table S5.

The MMRM analysis of adjusted mean change indicated gradual improvements in global health, functional scales, and esophageal cancer-specific symptoms during and after treatment. However, fatigue and appetite loss worsened during treatment but were alleviated afterwards (Supplementary Fig. S6). Improvements on PROs from baseline to 12 months after CCRT were observed overall: fatigue (MMRM-adjusted mean change −7.21 [95% CI −12.50 to −1.92] in cohort A-60Gy and −19.02 [−24.42 to −13.63] in cohort B-50Gy), appetite loss (−7.63 [−16.52 to 1.26] and −14.11 [−23.18 to −5.04]), dysphagia (−24.48 [−28.37 to −20.60] and −25.19 [−29.16 to −21.22]), pain (−15.26 [−18.06 to −12.45] and −16.74 [−19.59 to −13.89]; assessed with QLQ-OES18), choking (−15.79 [−22.10 to −9.48] and −18.46 [−24.92 to −12.01]), physical function (7.65 [3.27–12.05] and 11.25 [6.77–15.74]), emotional function (10.78 [4.84–16.72] and 15.11 [9.04–21.18]) and global health status (9.74 [6.14–13.34] and 15.37 [11.70–19.03]) (Supplementary Tables S6 and S7).

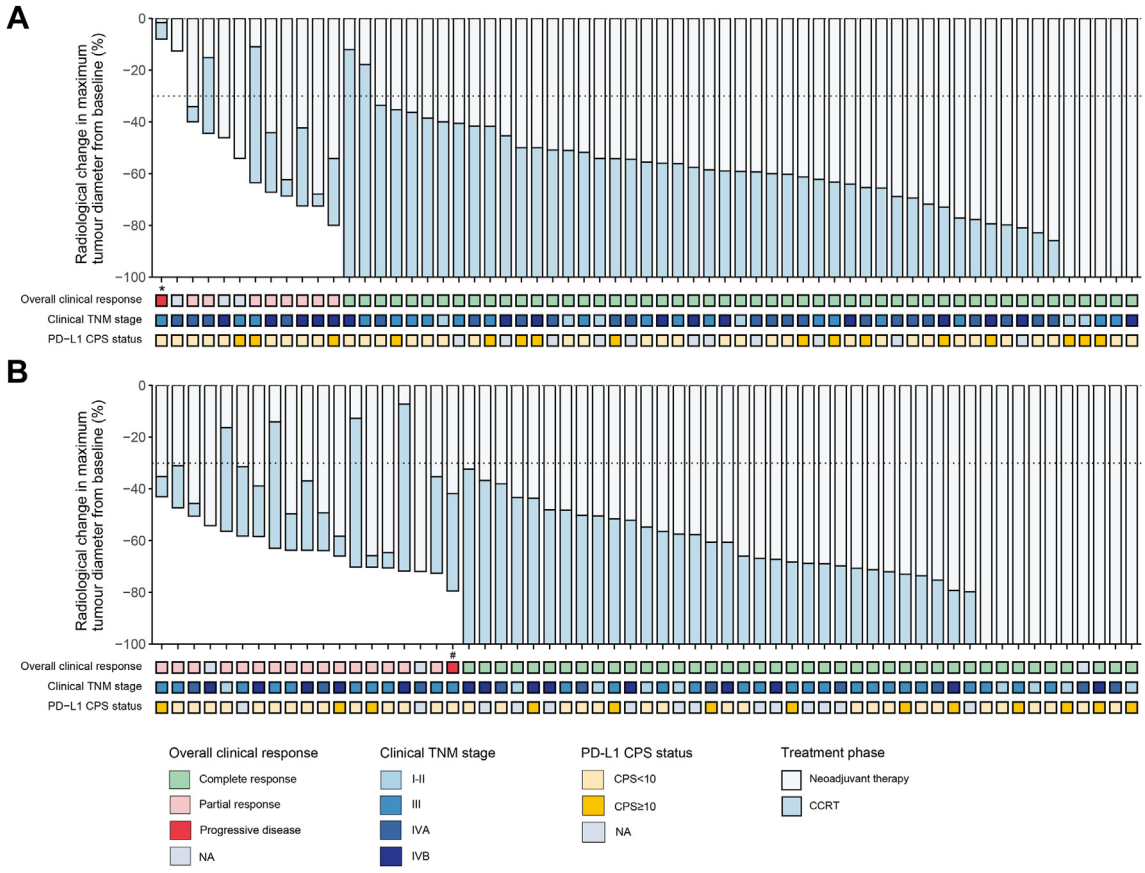


*Fig. 2:* **Tumor responses of patients in each cohort.** Maximum change in tumor size from baseline assessed according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) in (A) cohort A-60Gy and (B) cohort B-50Gy. The dotted line at −30% represents partial response. * The patient achieved stable disease of previous lesion after treatment, but bone metastasis was detected 2 months after CCRT. # The patient with upper thoracic ESCC achieved a partial response of previous lesion after treatment, but a second lesion in the middle thoracic region was identified at 2 months after CCRT. Abbreviation: CCRT, concurrent chemoradiotherapy; CPS, combined positivity score; ESCC, esophageal squamous cell carcinoma.

## Exploratory analysis

We explored the relationship between PD-L1 CPS scores and tumor response rate after neoadjuvant therapy, as well as PFS and OS. The results are presented in Supplementary Fig. S7 and Tables S8–S11 in the Supplementary materials. CR rate after neoadjuvant

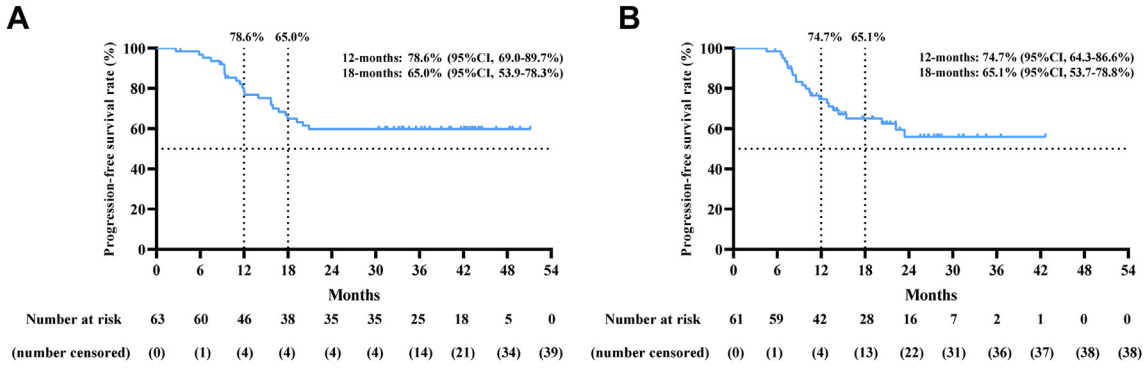


*Fig. 3:* **Kaplan–Meier estimates of progression-free survival in (A) cohort A-60Gy and (B) cohort B-50Gy.**

| Toxicity, n (%) | Cohort A-60Gy (N = 63) | | | | | Cohort B-50Gy (N = 61) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | G0-1 | G2 | G3 | G4 | G5 | G0-1 | G2 | G3 | G4 | G5 |
| ALT elevation | 57 (90.4) | 3 (4.8) | 2 (3.2) | 1 (1.6) | 0 | 57 (93.4) | 4 (6.6) | 0 | 0 | 0 |
| AST elevation | 58 (92.0) | 3 (4.8) | 1 (1.6) | 1 (1.6) | 0 | 59 (96.7) | 2 (3.3) | 0 | 0 | 0 |
| Anemia | 46 (73.0) | 17 (27.0) | 0 | 0 | 0 | 49 (80.4) | 11 (18.0) | 1 (1.6) | 0 | 0 |
| Bilirubin elevation | 62 (98.4) | 1 (1.6) | 0 | 0 | 0 | 58 (95.1) | 3 (4.9) | 0 | 0 | 0 |
| Cough | 55 (87.3) | 7 (11.1) | 1 (1.6) | 0 | 0 | 56 (91.8) | 5 (8.2) | 0 | 0 | 0 |
| Constipation | 63 (100) | 0 | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Diarrhea | 59 (93.6) | 3 (4.8) | 1 (1.6) | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Esophagitis | 29 (46.0) | 24 (38.1) | 10 (15.9) | 0 | 0 | 32 (52.5) | 24 (39.3) | 5 (8.2) | 0 | 0 |
| Esophageal fistula | 62 (98.4) | 1 (1.6) | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Esophageal stenosis | 54 (85.7) | 9 (14.3) | 0 | 0 | 0 | 56 (91.8) | 5 (8.2) | 0 | 0 | 0 |
| Fatigue | 53 (68.2) | 17 (27.0) | 3 (4.8) | 0 | 0 | 51 (83.6) | 9 (14.8) | 1 (1.6) | 0 | 0 |
| Fever | 61 (96.8) | 2 (3.2) | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Hypertriglyceridaemia | 62 (98.4) | 1 (1.6) | 0 | 0 | 0 | 57 (93.4) | 4 (6.6) | 0 | 0 | 0 |
| Hypothyroidism | 61 (96.8) | 2 (3.2) | 0 | 0 | 0 | 58 (95.1) | 3 (4.9) | 0 | 0 | 0 |
| Immuno-related hepatitis | 61 (96.8) | 0 | 1 (1.6) | 1 (1.6) | 0 | 61 (100) | 0 | 0 | 0 | 0 |
| Leukopenia | 40 (63.5) | 21 (33.3) | 2 (3.2) | 0 | 0 | 46 (75.4) | 14 (23.0) | 1 (1.6) | 0 | 0 |
| Lymphopenia | 0 | 5 (8.0) | 29 (46.0) | 29 (46.0) | 0 | 1 (1.6) | 12 (19.7) | 41 (67.2) | 7 (11.5) | 0 |
| Nausea or vomiting | 55 (87.3) | 7 (11.1) | 1 (1.6) | 0 | 0 | 55 (90.2) | 5 (8.2) | 1 (1.6) | 0 | 0 |
| Neutropenia | 55 (87.3) | 5 (7.9) | 3 (4.8) | 0 | 0 | 54 (88.5) | 2 (3.3) | 4 (6.6) | 1 (1.6) | 0 |
| Neuropathy | 62 (98.4) | 1 (1.6) | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Pneumonitis | 58 (92.0) | 2 (3.2) | 2 (3.2) | 0 | 1 (1.6) | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Radiation dermatitis | 58 (92.0) | 4 (6.4) | 1 (1.6) | 0 | 0 | 58 (95.1) | 3 (4.9) | 0 | 0 | 0 |
| Rash | 59 (93.6) | 4 (6.4) | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Tracheal fistula | 63 (100) | 0 | 0 | 0 | 0 | 60 (98.4) | 1 (1.6) | 0 | 0 | 0 |
| Thrombocytopenia | 53 (84.1) | 10 (15.9) | 0 | 0 | 0 | 57 (93.4) | 4 (6.6) | 0 | 0 | 0 |
| Upper gastrointestinal bleeding | 61 (96.8) | 2 (3.2) | 0 | 0 | 0 | 61 (100) | 0 | 0 | 0 | 0 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Table 3:* **Treatment-related adverse events.**

therapy was higher in patients with a PD-L1 CPS of 10 or higher compared to those with a PD-L1 CPS below 10 in both cohorts (19% vs. 6% in cohort A-60Gy; 31% vs. 18% in cohort B-50Gy), although the difference was not statistically significant. In addition, no significant association was observed between PD-L1 CPS and PFS or OS. We also compared the CR rates and survival outcomes between the higher and lower PD-L1 expression groups using CPS cutoff values of 1, 5, and 20. Similar to the findings with a cutoff of 10, no significant differences were found.

The potential impact of tumor response after neoadjuvant chemo-immunotherapy on survival outcomes was also explored as a post-hoc analysis. Overall, patients with SD after neoadjuvant therapy had a lower 18-month PFS rate compared to those who achieved CR or PR (20.0% vs. 68.6%, $P < 0.0001$, HR = 6.261, 95% CI, 2.996–13.082). Specifically, for patients with SD following neoadjuvant therapy, the 18-month PFS rates were 16.7% and 25.0% for cohort A-60Gy and cohort B-50Gy, respectively. In patients with PR or CR after neoadjuvant therapy, the 18-month PFS rates were 70.1% and 67.9% for cohort A-60Gy and cohort B-50Gy, respectively (Supplementary Fig. S8).

## Discussion

In this phase II, two-cohort study, neoadjuvant toripalimab plus chemotherapy followed by radiotherapy and concurrent capecitabine demonstrated robust antitumor activity and a tolerable safety profile in patients with locally advanced ESCC. The 18-month PFS rates were 65.0% in cohort A-60Gy and 65.1% in cohort B-50Gy. The ORR was encouraging, with 90.5% in cohort A-60Gy and 93.4% in cohort B-50Gy after neoadjuvant therapy, and 93.7% in cohort A-60Gy and 93.4% in cohort B-50Gy after radiotherapy and concurrent capecitabine. The ≥G3 pneumonitis occurred in 4.8% of patients in cohort A-60Gy, while no ≥G3 pneumonitis occurred in cohort B-50Gy. We found that neoadjuvant chemoimmunotherapy followed by radiotherapy and concurrent capecitabine led to significant improvements on PROs from baseline to 12 months after CCRT.

The survival results in this study were promising compared to the PFS and LRFS data reported in previous studies evaluating definitive CCRT in ESCC. The 1-year PFS was 78.6% in cohort A-60Gy and 74.7% in cohort B-50Gy, compared to 40% in ACCORD 17,[4] 60% in ARTDECO[8] and 66% in Eso-shanghai2 trial.[9] The use of neoadjuvant chemo-immunotherapy appears to be

the key factor contributing to the significant survival benefit observed in our study. In the current study, neoadjuvant chemo-immunotherapy substantially reduced tumor volume, with an ORR of 90.5% in cohort A-60Gy and 93.4% in cohort B-50Gy, and a median relative change in the maximum diameter of 56.1% and 58.3%, respectively. Large primary tumor volume has been identified as a poor prognostic factor in ESCC treated with definitive CCRT.[21,22] Tumor reduction before CCRT was meaningful for the improved local control and survival. Furthermore, immunotherapy also modulates the tumor microenvironment by activating antitumor T cells, normalizing tumor vessels and reducing tumor hypoxia, thereby increasing radiosensitivity.[23]

Although the ORR after neoadjuvant chemo-immunotherapy was substantial in current study, the CR rates, assessed by the RECIST criteria, were lower than the reported pathological complete response (pCR) rates of 20%–40% in resectable ESCC after neoadjuvant chemo-immunotherapy.[14–17] This discrepancy highlights the challenge of accurate restaging following neoadjuvant therapy. Restaging is crucial for therapeutic decision-making and determining patient prognosis in ESCC; however, it is complicated by treatment-induced fibrosis and ulceration, which can obscure the interpretation of radiological images. Previous studies have indicated that anatomical responses may be weeks or even months later than metabolic responses. As a result, some patients evaluated as PR with RECIST presented pCR on postoperative pathology.[24] According to the National Comprehensive Cancer Network (NCCN) guidelines, PET, CT, and endoscopic ultrasonography are recommended for restaging in resectable patients prior to surgery. These diagnostic tests complement each other in the restaging of ESCC. In particular, PET plays a pivotal role due to its sensitivity in predicting pCR and its ability to detect interval distant metastases, offering an advantage over CT.[25,26] In our study, the accuracy of restaging was limited by the omission of PET from the process, primarily due to its high cost, which is not covered by insurance.

One of the main challenges of CCRT for patients with ESCC is minimizing the adverse effects, which often affect treatment completion and survival. Despite a high percentage of stage IV tumors, toxicity was mild in the current study, particularly in the 50Gy cohort. The tolerability of the current combination treatment can be attributed to the use of neoadjuvant chemo-immunotherapy before CCRT, and the administration of oral capecitabine during radiotherapy instead of intravenous dual-drug chemotherapy. Chemo-immunotherapy effectively alleviated dysphagia before CCRT, thereby improving the patient's nutritional status and helping to reduce the toxicity of subsequent CCRT. Furthermore, it is known that a bulky tumor is associated with a high risk of fatal events, such as esophageal fistula, bleeding and severe pneumonitis.[27–29] Neoadjuvant therapy can mitigate these risks by reducing the tumor volume subject to the subsequent CCRT. Capecitabine, oral prodrug of fluorouracil, is converted to fluorouracil in tumor tissues. A recent phase III study showed that capecitabine resulted comparable efficacy but better tolerability than fluorouracil plus cisplatin in definitive CCRT for inoperable ESCC.[10] Therefore, capecitabine alone may be considered as an alternative to the intravenous dual-drug chemotherapy in CCRT, particularly for patients who have achieved CR or PR after neoadjuvant chemo-immunotherapy.

The patterns of combinations of CCRT and immunotherapy is now a study focus for ESCC. Preliminary data from some single-arm studies have shown promising efficacy and safety profiles of CCRT in combination with concomitant or/and adjuvant immunotherapy in unresectable locally advanced ESCC.[30,31] Prospective phase III clinical trials (such as ESCORT-CRT, KEYNOTE-975, KUNLUN, RATIONALE-311, SKYSCRAPER-07)[32] are on-going to confirm the effectiveness of these combination treatments. Administering immunotherapy in the neoadjuvant setting, with a less compromised immune system and intact tumors, may stimulate a more robust activation of antitumor T cells, potentially improving clinical outcomes.[33] A recent sing-arm phase II study evaluated the efficacy of sintilimab plus chemotherapy followed by CCRT (radiation at 50.4Gy and concurrent weekly carboplatin and paclitaxel).[34] It achieved a 2-year local control rate of 81.7%, a 1-year and 2-year PFS rates of 72% and 61.3%. Other than the promising survival and safety profiles, the current study also showed high treatment compliance of the combination regimen. There were 61 (96.8%) patients in cohort A-60Gy and 60 (98.4%) patients in cohort B-50Gy who completed neoadjuvant therapy, while there were 60 (95.2%) patients in cohort A-60Gy and 61 (100%) patients in cohort B-50Gy who completed definitive CCRT.

The current study used a two-cohort design to evaluate the efficacy and safety of different radiation dose on survival following neoadjuvant therapy. At the time of study initiation, there was still controversy regarding whether radiotherapy dose escalation improved survival in patients with ESCC receiving CCRT. With the promising antitumor efficacy of immunotherapy in combination with chemotherapy as first-line treatment for advanced ESCC and as neoadjuvant therapy in resectable cases, we hypothesized that a robust response to neoadjuvant chemo-immunotherapy might allowed for a reduction in the intensity of subsequent CCRT. However, it remained uncertain whether 60 or 50Gy would be the optimal dose. Consistent with the recent phase III studies evaluating dose escalation in esophagus cancer,[8,13] our results showed that the two cohorts achieved similar LRFS as well as PFS. In terms of toxicities, the incidence of $\geq$ G3 pneumonitis was higher in the 60Gy cohort (4.8% vs. 0), as was the incidence of $\geq$ G3 esophagitis (15.9% vs. 8.2%) and lymphopenia (92.0% vs. 78.7%).

Therefore, based on our results, following neoadjuvant chemo-immunotherapy, patients receiving 50Gy of radiotherapy demonstrated better tolerability without compromising treatment effectiveness.

The potential impact of tumor response after neoadjuvant chemo-immunotherapy on survival outcomes was also analyzed. Overall, patients with SD after neoadjuvant therapy had a lower PFS rate compared to those who achieved CR or PR (20.0% vs. 68.6%, HR = 6.261, 95% CI, 2.996–13.082). This suggests an increased risk of disease progression with clinical importance, raising the question of whether the subsequent radiation dose should be tailored based on the response to neoadjuvant therapy. Specifically, in patients with SD following neoadjuvant therapy, the 18-month PFS rate was not improved in cohort A-60Gy than cohort B-50Gy (16.7% vs. 25.0%). These findings suggest that the response to neoadjuvant therapy could predict the efficacy of subsequent CCRT. However, escalating the dose to 60Gy did not overcome treatment resistance in patients with SD after neoadjuvant therapy. However, we cannot draw firm conclusions due to the small number of non-responders in the current study.

PROs capture the patients' perspective on their symptoms, functioning, and health-related quality of life, offering important complementary data to the efficacy and safety outcomes. This is particularly crucial for patients with unresectable ESCC who typically experience a high symptom burden and low baseline functioning. In our study, we observed improvements in global health, functional scales, and esophageal cancer-specific symptoms from baseline to 12 months post-CCRT in both cohorts, particularly in dysphagia, pain, and choking symptoms. Most of these improvements were clinically important with a mean difference exceeding 10 points,[35] especially in cohort B. These results align with the promising efficacy and tolerability of the treatment.

PD-L1 expression is a critical biomarker for immunotherapy in ESCC and plays a key role in treatment decisions. The KEYNOTE-181 Study demonstrated that high PD-L1 levels (CPS ≥10) are associated with improved survival with pembrolizumab in advanced esophageal cancer.[36] Similarly, the ESCORT study found that camrelizumab provided survival benefits across all PD-L1 levels, with greater advantages for those with higher expression (CPS ≥1).[37] However, the role of PD-L1 as a biomarker is less clear when immunotherapy is combined with chemotherapy. The relationship between PD-L1 expression and pathological response to neoadjuvant immunotherapy remains controversial. Some studies have found no significant correlation between PD-L1 status and pathological response,[38–40] while the ESCORT-NEO study reported a significant pCR advantage in patients with higher PD-L1 expression receiving neoadjuvant chemo-immunotherapy.[17] In our study, 60.4% of the patients exhibited PD-L1 CPS ≥1, aligning with the findings from the ESCORT-NEO study (55.2%). Our analysis did not show a significant association between PD-L1 CPS and either the CR rate after neoadjuvant therapy or survival outcomes, though a trend towards higher CR rates and longer PFS was observed in patients with PD-L1 CPS ≥10. Further validation is needed to determine whether PD-L1 expression can reliably predict long-term survival.

This study has several limitations. Firstly, it is limited by its non-randomized and single-arm design. Further randomized studies are warranted to verify the efficacy. Second, the follow-up duration remained relatively short. With a mean follow-up of 21.5 months (IQR, 16.3–27.4 months) in cohort B, the 18-month PFS data remains immature, and longer follow-up is needed to validate the efficacy of a 50Gy radiation dose following neoadjuvant chemo-immunotherapy. Thirdly, despite controlling for several measured variables, the presence of unmeasured confounders remains a concern. These could include underlying comorbidities, lifestyle factors, psychological or socioeconomic factors, which were not included in the analysis but may still affect the outcomes. Future studies with more comprehensive data collection, including these variables, could help mitigate this limitation.

In conclusion, the combination of neoadjuvant chemo-immunotherapy, radiotherapy and concurrent capecitabine achieved promising ORR and efficacy in patients with locally advanced ESCC. Further investigation is warranted.

#### Contributors

YH, BQ, and HL were responsible for the conception and design. FL, DW, YR, and SW were responsible for provision of study materials or patients. FL, DW, YR, SW, YS, MW, HZ, PZ, SZ, SY, and CX were responsible for collection and assembly of data. FL, DW, YR, and SW were responsible for data analysis and interpretation. All authors were involved in writing and revising the manuscript. All authors participated in reviewing and editing of the manuscript, and approved the final version before submission. Three principal investigators (FL, BQ, and HL) verified the raw data and had final responsibility for the decision to submit the manuscript for publication. FL, DW, YR, and SW contributed equally.

#### Data sharing statement

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

#### Declaration of interests

We declare no competing interests.

#### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103184.

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