Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2025, Volume 5, Issue 1, Page No: 232-242

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Real-World Effectiveness of Anti–PD-1 Immunotherapy Combined with Definitive Chemoradiotherapy in Inoperable ESCC: A Multicenter Weighted Analysis

Wei Chen[1]*, Li Zhang[1]

[1]Department of Clinical Oncology and Cancer Medicine, Faculty of Medicine, Peking University, Beijing, China.

***E-mail** ✉ wei.chen@outlook.com

Received: 27 January 2025; **Revised:** 18 April 2025; **Accepted:** 19 April 2025

ABSTRACT

The unclear benefit of supplementing definitive chemoradiotherapy (dCRT) with immune checkpoint inhibitors (ICIs) for unresectable esophageal squamous cell carcinoma (ESCC) warrants investigation into whether the timing of immunotherapy during the peri-dCRT window shapes survival. Patients with non-resectable ESCC who received dCRT plus ICIs between April 2018 and April 2022 were enrolled at five Chinese hospitals. A historical reference arm receiving dCRT only was used for benchmarking. Stabilized inverse probability of treatment weights (sIPTW) techniques were applied to contrast survival endpoints. Both efficacy metrics and treatment-emergent toxicities were appraised. The study cohort included 290 patients with inoperable ESCC managed with dCRT+ICI. Over a median observation period of 35.7 months, 1- and 2-year overall survival (OS) figures were 86.7% and 66.9%, respectively, whereas 1- and 2-year progression-free survival (PFS) were 66.7% and 47.3%, respectively. Median PFS was recorded at 22.4 months; median OS remained undefined. The dCRT+ICI arm demonstrated meaningfully longer OS than the historical comparator (2-year OS: 66.9% versus 56.5%; sIPTW-weighted analysis: HR = 0.62, P < .001). After sIPTW adjustment, OS did not diverge among the induction, concurrent, and consolidation cohorts. The sIPTW-weighted evaluation revealed that both the induction and concurrent cohorts achieved significantly longer PFS than the consolidation cohort. Combining immunotherapy with dCRT improved survival and maintained a tolerable toxicity profile in inoperable ESCC. Deploying immunotherapy during induction or concurrent phases may yield a greater survival benefit than consolidation-phase administration.

Keywords: Immunotherapy, Definitive chemoradiotherapy, Inoperable esophageal cancer, Real-world study, PD-L1

How to Cite This Article: Chen W, Zhang L. Real-World Effectiveness of Anti–PD-1 Immunotherapy Combined with Definitive Chemoradiotherapy in Inoperable ESCC: A Multicenter Weighted Analysis. Asian J Curr Res Clin Cancer. 2025;5(1):232-42. https://doi.org/10.51847/eA665c6fIw

Introduction

Esophageal cancer ranks among the most frequent alimentary tract malignancies. Squamous cell carcinoma, its chief pathological variant, represents roughly 90% of esophageal cancer diagnoses in China [1, 2]. Landmark RTOG 8501 and RTOG 9405 investigations cemented definitive chemoradiotherapy (dCRT) as the benchmark intervention for non-resectable locally advanced esophageal squamous cell carcinoma (LA-ESCC), yielding 2-year overall survival (OS) of 38%–40% and 5-year OS of 26% [3-5]. Subsequent radiotherapy innovations—intensity-modulated radiation therapy, volumetric-modulated arc therapy, and helical tomotherapy—coupled with socioeconomic gains (such as improved nutritional status) have raised LA-ESCC survival rates in China. For example, an earlier nationwide multicenter real-world study of inoperable ESCC receiving dCRT across China between 2015 and 2016 documented 2-year and 5-year OS of 50% and 30%, respectively [6]. Likewise, findings from another prospective randomized phase III trial on LA-ESCC care (ESO-shanghai1, paclitaxel/5-FU vs. cisplatin/5-FU-based dCRT) showed a 2-year OS of 60.6%–61.5% and a 5-year OS of 40.8%–44.3% [7]. Still,

the long-term outlook for patients with unresectable ESCC remains discouraging. Hence, more potent treatment avenues are urgently required for this group.

Multiple prospective randomized controlled phase III trials have established that combining immune checkpoint inhibitors (ICIs) with chemotherapy improves outcomes in advanced esophageal cancer, positioning ICIs as the new benchmark for first-line therapy [8-11]. Within LA-ESCC, a handful of prospective single-arm explorations of modest scale have signaled that dCRT integrated with ICIs (dCRT+ICIs) carries acceptable tolerability and encouraging activity (2-year OS: 50.0%–75.0%) [12-14]. In particular, corroborated by several phase III datasets, PD-1 inhibitors, alongside chemotherapy, now define the standard of first-line treatment for advanced esophageal cancer [8-11].

Regarding optimal immunotherapy scheduling for patients undergoing dCRT+ICI, the PACIFIC trial demonstrated that dCRT followed by consolidation immunotherapy (delivered post-CRT to eradicate residual malignant cells) enhanced survival in non-small cell lung cancer (NSCLC) compared with dCRT alone. By contrast, the PACIFIC-2 study found that concurrent immunotherapy did not yield favorable outcomes [15]. Conversely, a retrospective clinical analysis showed that, across 758 patients with 1,798 lesions, the concurrent immunoradiotherapy schema yielded the greatest effectiveness. Specifically, concurrent immunoradiotherapy prolonged OS by approximately 9 months, with the greatest benefit when immunotherapy was initiated at least 1 month before radiotherapy [16]. Other reports suggest that induction immunotherapy administered before radiotherapy can foster vessel normalization and mitigate hypoxia, augmenting radiosensitivity within locally advanced esophageal cancer [17]. The ideal point at which to interweave immunotherapy with radiotherapy, therefore, remains unsettled. At present, the majority of prospective phase III protocols are based on concurrent and consolidation immunotherapy designs, such as Keynote-975, KUNLUN, and RATIONALE-311 [18-20]. Moreover, the SKYSCRAPER07 trial layout embeds consolidation immunotherapy [21]. Outcomes from these clinical efforts may yield insights to steer decision-making on immunotherapy-radiotherapy sequencing.

In light of the current evidence landscape and persisting gaps in the use of dCRT+ICI for ESCC outlined above, this study pursues two aims: (1) to gauge whether incorporating PD-L1 as an ICI alongside dCRT additionally ameliorates survival in inoperable ESCC and (2) to probe how disparate immunotherapy launch windows affect prognosis.

Materials and Methods

Study design and participants

Records were sourced from individuals undergoing dCRT together with PD-1 blockade at five Chinese hospitals spanning April 2018 through April 2022. The data lock point for follow-up was April 2024. Enrollment required meeting every one of the following conditions: (1) ESCC confirmed via histology or cytology; (2) surgery not feasible because of unresectable extent, operative risk factors, or the patient's decision to forgo resection; (3) M1 status restricted exclusively to supraclavicular lymph node deposits (classified according to the 8th edition of the American Joint Committee on Cancer); (4) PD-1 blockade-based immunotherapy introduced either before, during, or after dCRT; (5) receipt of a minimum of one cycle each of immunotherapy and chemotherapy inside the peri-radiation period; (6) a radiotherapy dose to the primary tumour equalling or exceeding 50 Gy; and (7) full retrievability of clinical data. Cases were excluded based on (1) another invasive malignancy, apart from melanoma, registered within the past 5 years; (2) distant dissemination beyond regional nodes into visceral sites; and (3) prior radiotherapy delivered to the thorax.

To afford a comparison of efficacy gains from appending ICIs to dCRT, a historical reference arm was abstracted from an earlier observational analysis conducted across 14 Chinese centres that captured survival figures for inoperable ESCC patients given dCRT alone during 2015–2016.6 Following the screening pathway shown in **Figure 1**, of an initial pool of 3,060 candidates, 994 were removed for the reasons listed: 159 because 2D/3D radiation technology had been employed and 835 owing to the absence of any chemotherapy. The final historical control set comprised 2,066 pooled patients.

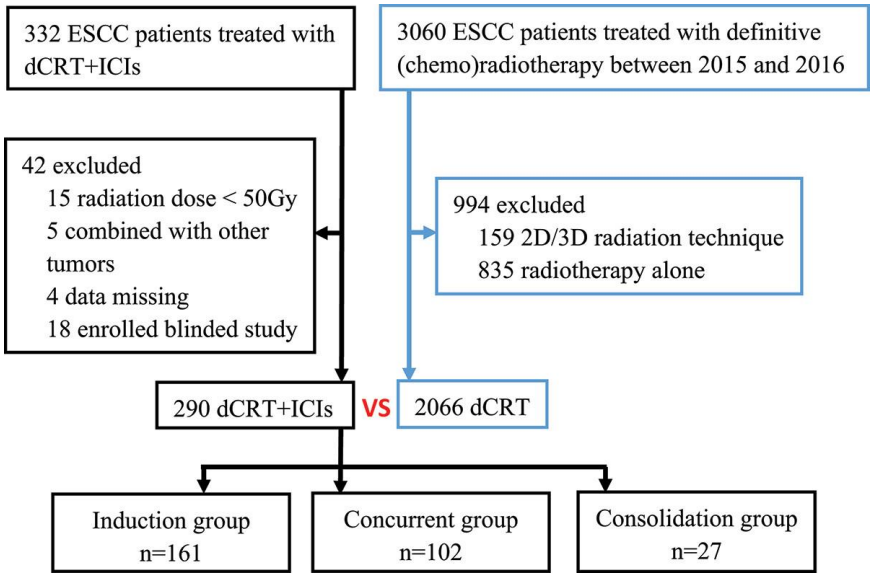


Figure 1. Flow chart depicting patient selection and grouping. Abbreviations: ESCC = Esophageal Squamous Cell Carcinoma, dCRT = definitive chemoradiotherapy, ICIs = Immune checkpoint inhibitors.

Approval for this work was provided by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and all procedures conformed to the 2013 revision of the Declaration of Helsinki. Written consent was waived, given the framework's retrospective nature. The trial is registered on ClinicalTrials.gov (Trial no. NCT04821778).

Treatment

The peri-radiation interval was defined as the period from the initiation of chemoimmunotherapy to 6 months before radiation, and lasting until 3 months after its completion. Patients assigned to the induction subset had concluded one or more immunotherapy cycles before radiation commenced. The concurrent subset included those who received immunotherapy during radiotherapy, while the consolidation subset included those who received immunotherapy after radiation had finished.

Most chemotherapy backbones relied on a taxane combined with a platinum agent as a doublet. Radiotherapy techniques included intensity-modulated radiation therapy, volumetric-modulated arc therapy, and helical tomotherapy; all subjects were treated using conventional fractionation with daily doses ranging from 1.8 to 2.14 Gy. Total radiotherapy time ranged from 35 to 60 days. Toxicities linked to treatment (TRAEs) were graded in line with the Common Terminology Criteria for Adverse Events, version 5.0 (US National Institutes of Health, Bethesda, Maryland).

Statistical analyses

OS was measured from the start of the initial chemoimmunotherapy or radiotherapy to death from any cause. For patients still alive or whose status could not be traced, OS was censored at the last known survival time. PFS was captured from therapy initiation until the earliest of locoregional progression, distant metastasis, or death from any cause. For individuals without events or lost to monitoring, PFS was censored at the last evaluation, confirming no progression. Propensity scores were modeled using multinomial logistic regression. The covariates accounted for comprised tumor location, tumor length, T category, N category, and ICI cycle count. Cases with missing covariate values were addressed through multiple imputation. Stabilized inverse probability of treatment weighting (sIPTW) was subsequently applied using the propensity scores generated. Balance was assessed using standardized mean differences (SMDs) within the weighted sample across treatment subgroups. A criterion of SMD below 0.1 was adopted to indicate an appropriate balance, consistent with recommended practice [22], and applied to the sIPTW-adjusted data as well. Survival distributions were plotted using Kaplan-Meier estimates, and follow-up duration was determined via the reverse Kaplan-Meier method. Inter-cohort disparities in OS and PFS were scrutinized using an unstratified log-rank test. Hazard ratios (HRs) alongside 95% confidence intervals (CIs) were extracted from a Cox proportional hazards model applying Efron's tie-handling technique. All statistical

work was conducted in R, version 4.3.1 (R Foundation) and SPSS, version 24.0 (IBM Institute Inc). Every reported p-value was two-tailed, and values below the .05 threshold were taken to indicate statistical significance.

Results and Discussion

Baseline characteristics

Screening took place from April 2018 to April 2022 across five Chinese centers, yielding an initial pool of 332 individuals, of whom 42 were disqualified. The remaining 290 constituted the study population **(Figure 1).** Males accounted for 236 (81.4%); the median age at enrolment was 65 years (range, 40–85 years); and 151 patients (52.1%) presented with stage III disease, while 108 (37.3%) had stage IV disease.

The median radiation dosage delivered was 50.4 Gy (range, 50–69.96 Gy), and patients received a median of 5 immunotherapy infusions (range, 1–29). The induction, concurrent, and consolidation groupings comprised 161 (55.5%), 102 (35.2%), and 27 (9.3%) individuals, respectively. Among those in the induction category, a median of 3 pre-radiotherapy immune cycles had been administered (range, 2–8), with a median of 56 days (range, 24–180) between the start of radiation and the start of the immune cycles. In the consolidation category, the median number of immune cycles was 6 (range, 1–23), with a median span of 44 days (range, 3–92) from the first immunotherapy dose to the completion of radiotherapy.

Chemotherapy was given over a median of 5 cycles (range, 1–19). A total of 186 patients (64.1%) had chemotherapy before radiation started. During and after the radiation course, 240 (82.8%) and 63 (21.7%) patients underwent concurrent and consolidation chemotherapy, respectively **(Table 1).**

Table 1. Characteristics of patients (n = 290).

Characteristic	N (%)
Median age (range), year	65 (40–85)
Sex	
Male	236 (81.4)
Smoking history	
No	158 (54.5)
Yes	132 (45.5)
Drinking history	
No	162 (55.9)
Yes	128 (44.1)
ECOG score	
0–1	253 (87.2)
2	37 (12.8)
Median BMI (IQR, range)	22.9 (20.8–25.1)
Tumor location	
Upper	128 (44.1)
Middle	119 (41.0)
Lower	43 (14.9)
Median tumor length (IQR, range), cm	5.0 (4.0–7.0)
Clinical T stage	
T1–2	117 (40.3)
T3–4	173 (59.7)
Clinical N stage	
N0	17 (5.9)
N1	89 (30.7)
N2	126 (43.4)
N3	58 (20.0)
Clinical M stage	
M0	250 (86.2)
M1	40 (13.8)
Clinical TNM stage	
I-II	31 (10.6)
III	151 (52.1)

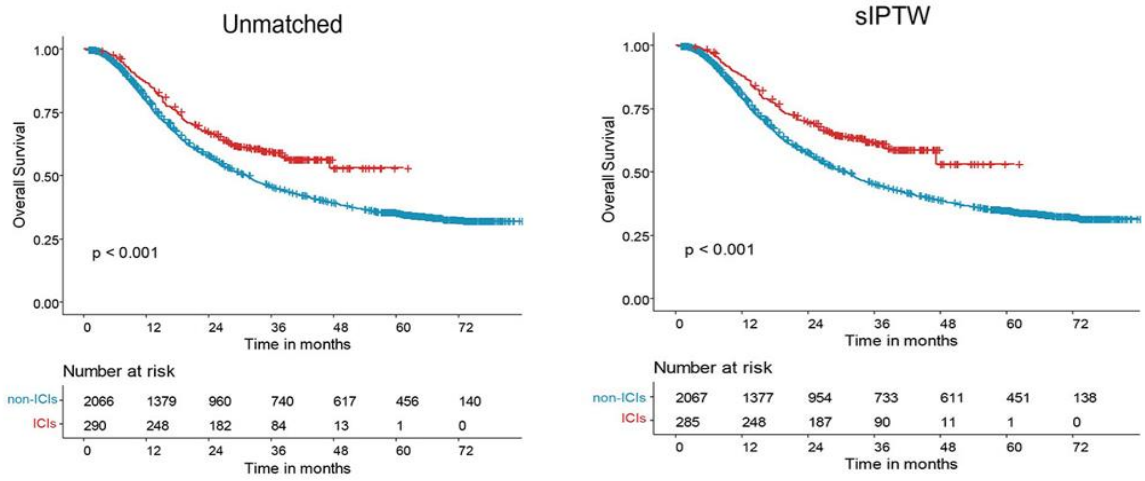
IV	108 (37.3)
ICIs cycle	
1–2	85 (29.3)
3–4	56 (19.3)
5–6	31 (10.7)
≥7	118 (40.7)
Timing of initiation of ICIs	
Before radiation	161 (55.5)
Concurrent radiation	102 (35.2)
After radiation	27 (9.3)
Radiation dosage	
50 Gy	35 (12.1)
>50 Gy	255 (87.9)
Timing of chemotherapy usage	
Before radiation	186 (64.1)
Concurrent radiation	240 (82.8)
After radiation	63 (21.7)

Abbreviation: IQR = interquartile range, BMI = body mass index, ECOG = Eastern Cooperative Oncology Group, ICIs = immune checkpoint inhibitors.

Survival outcomes

With the data frozen in April 2024, the median observation period extended to 35.7 months (95% CI: 34.5–36.9). The proportion of patients alive at the 1-year landmark was 86.7% (95% CI: 82.9–90.8), dipping to 66.9% (95% CI: 61.6–72.6) at 2 years. The corresponding figures for those free from progression were 66.7% (95% CI: 61.5–72.4) at 1 year and 47.3% (95% CI: 41.9–53.5) at 2 years. The median OS endpoint was not yet estimable, whereas the median PFS was 22.4 months (95% CI: 18.4–26.8).

Juxtaposed with the historical control cohort, the dCRT+ICI arm achieved a noteworthy OS gain (HR = 0.67; 95% CI: 0.56–0.82; P < .001) **(Figure 2a).** After employing sIPTW to match the two populations on age, sex, and clinical TNM staging, the adjusted OS advantage for the dCRT+ICI group persisted (HR = 0.62; 95% CI: 0.50–0.75; P < .001) **(Figure 2b).**



a) b)

Figure 2. Overall survival data are illustrated in the definitive chemoradiotherapy combined with immune checkpoint inhibitor population compared before (a) and after sIPTW (b). Abbreviations: sIPTW = stabilized inverse probability of treatment weighting.

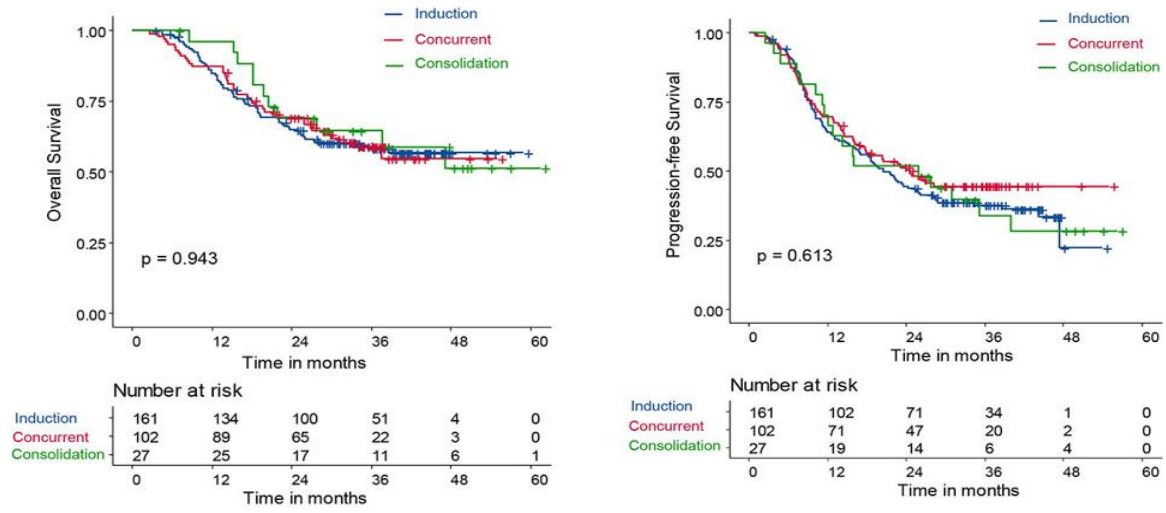
Univariate and multivariate Cox regression analyses of OS and PFS

Exploratory univariate testing flagged several variables as significantly associated with abbreviated OS: tumor length > 5 cm, T3–4 classification, N2–3 classification, and an ICI cycle count < 4. Likewise, prior alcohol use, T3–4 status, N2–3 status, and ≤ 4 ICI cycles were each significantly correlated with inferior PFS. Multivariable

modeling subsequently confirmed that N2–3 nodal status and receipt of 4 or fewer ICI cycles were independent predictors of unfavorable OS and PFS.

Effect of immunotherapy intervention time on survival outcomes

When subjects were segregated according to whether immunotherapy was introduced before (induction, 161 patients), during (concurrent, 102 patients), or after (consolidation, 27 patients) the radiation segment, pairwise contrasts of 1- and 2-year OS and PFS failed to yield curves that differed significantly. The OS probability at 1 and 2 years reached 84.8% (95% CI: 79.4–90.6) and 65.0% (95% CI: 57.9–72.9) in the induction arm; 87.3% (95% CI: 81.0–94.0) and 69.3% (95% CI: 60.9–78.9) in the concurrent arm; and 96.2% (95% CI: 89.0–100.0) and 69.0% (95% CI: 53.3–89.4) in the consolidation arm (P = .943) **(Figure 3a).** PFS rates at the same time points were 64.2% (95% CI: 57.1–72.1) and 44.7% (95% CI: 37.6–53.1) for induction; 69.6% (95% CI: 61.2–79.1) and 50.4% (95% CI: 41.5–61.2) for concurrent; and 70.4% (95% CI: 55.1–89.9) and 51.9% (95% CI: 36.1–74.6) for consolidation (P = .613) **(Figure 3b).** The median OS milestone was not attained in any of the three groups. Median PFS estimates were 20.5 months (95% CI: 16.9–26.1), 24.6 months (95% CI: 16.8–NR), and 25.8 months (95% CI: 12.8–NR) for the induction, concurrent, and consolidation cohorts, respectively.



a) b)

Figure 3. Overall survival and progression-free survival in the induction, concurrent, and consolidation groups (a) overall survival and (b) progression-free survival of patients with inoperable esophageal squamous cell carcinoma after immunotherapy combined with definitive chemoradiotherapy according to the timing of immunotherapy initiation.

sIPTW was subsequently harnessed to produce balanced background characteristics among the three timing strata. Following the application of sIPTW, PFS in both the induction and concurrent arms emerged as statistically superior to that in the consolidation arm (induction versus consolidation: HR = 0.441, P = .023; concurrent versus consolidation: HR = 0.429, P = .019). Direct comparison of the induction and concurrent arms did not uncover a significant PFS separation.

Treatment-related adverse events

Any-grade TRAEs were recorded in 119 of the 290 subjects (41.0%), with respective incidences of 33.5% (54/161), 55.9% (57/102), and 29.6% (8/27) across the induction, concurrent, and consolidation **subgroups (Table 2)**. Toxicities with a frequency exceeding 20% included leukopenia (81.5%), esophagitis (74.8%), neutropenia (71.4%), pruritus (44.5%), rash (43.7%), and hypothyroidism (21.0%). Grade 3–4 events affecting more than 10% of the overall cohort encompassed leukopenia (17.6%), esophagitis (12.6%), and neutropenia (10.9%). Within the induction subgroup, the leading severe toxicities were leukopenia (25.9%) and neutropenia (20.4%); within the concurrent subgroup, esophagitis (22.8%) and leukopenia (12.3%); and within the consolidation subgroup, pruritus (12.5%) and hypothyroidism (12.5%). Pneumonitis of grade 3–4 severity occurred in 3.7% and 8.8% of patients in the induction and concurrent arms, respectively, and in none in the

consolidation arm. Immune-related phenomena comprised hypothyroidism, hyperthyroidism, hyperglycemia, rash, and amylase elevation. The study documented zero fatalities ascribed to treatment.

Table 2. Treatment-related adverse events.

Treatment-related adverse events	Consolidation group n = 8 (%) Grade 3–4	Concurrent group n = 57 (%) Grade 3–4	Induction group n = 54 (%) Grade 3–4	Total n = 119 (%)
Leukopenia	0 (0.0)	7 (12.3)	14 (25.9)	97 (81.5)
Esophagitis	0 (0.0)	13 (22.8)	2 (3.7)	89 (74.8)
Neutropenia	0 (0.0)	2 (3.5)	11 (20.4)	85 (71.4)
Pruritus	1 (12.5)	3 (5.3)	1 (1.9)	53 (44.5)
Rash*	0 (0.0)	0 (0.0)	2 (3.7)	52 (43.7)
Hypothyroidism*	1 (12.5)	3 (5.3)	0 (0.0)	25 (21.0)
Hyperthyroidism*	0 (0.0)	2 (3.5)	1 (1.9)	20 (16.8)
Pneumonitis	0 (0.0)	5 (8.8)	2 (3.7)	18 (15.1)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.2)
Fever	0 (0.0)	1 (1.8)	1 (1.9)	15 (12.6)
Elevation in amylase*	0 (0.0)	0 (0.0)	0 (0.0)	13 (10.9)
Anorexia	0 (0.0)	0 (0.0)	0 (0.0)	10 (8.4)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.7)
Elevation in lipase*	0 (0.0)	0 (0.0)	0 (0.0)	8 (6.7)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.9)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.9)
Hepatitis	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.2)
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Adrenal insufficiency*	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)

*Considered immune-related adverse events.

Patterns of recurrence

By the analytic cut-off, the anatomical site of first treatment failure had been identified for 134 patients (46.2%). Locoregional recurrence alone was noted in 81 patients (27.9%), distant spread alone in 53 (18.3%), and simultaneous locoregional and distant failure in 12 (4.1%). The lung was the predominant distant landing site (25 patients, 8.6%), followed by the liver (13 patients, 4.5%) **(Table 3).**

Table 3. Pattern of first recurrence sites.

First site of recurrence	Patients with recurrent disease, n = 290, n (%)
Locoregional	93 (27.9)
Distant	53 (18.3)
Lung	25 (8.6)
Liver	13 (4.5)
Bone	7 (2.4)
Other sites	11 (3.8)
Both	12 (4.1)

As far as we are aware, the present work constitutes the first multicenter real-world appraisal of dCRT integrated with ICIs for non-resectable ESCC. Our results show that incorporating ICIs alongside dCRT, compared with a historical benchmark of dCRT-only treatment, extends OS while preserving a manageable safety profile in this patient group. When examining immunotherapy scheduling, after sIPTW balancing, PFS in both the induction and concurrent cohorts was significantly longer than in the consolidation cohort. Consequently, it seems that administering immunotherapy before or during the dCRT course yields greater benefit than reserving it for consolidation after dCRT has been completed.

Several other investigative teams have examined the contribution of dCRT paired with immunotherapy in inoperable esophageal carcinoma. For example, a phase Ib evaluation of concurrent dCRT plus sequential camrelizumab for LA-ESCC recorded a 2-year OS figure of 69.6% [12]. In another report, Park *et al*. [13] observed a 2-year OS of 75% among LA-ESCC and postoperative locally recurrent ESCC cases managed with concurrent and sequential durvalumab plus tremelimumab added to dCRT, versus 59.2% in a historical dCRT-only comparator. In a separate prospective phase II LA-ESCC study, Ai *et al*. [17] reported that induction chemoimmunotherapy followed by concurrent chemoradiotherapy yielded an exceptionally favorable 2-year OS of 77.2% and a model-predicted median OS of 80 months. The observations outlined above collectively imply that adding immunotherapy to dCRT significantly improves survival. In line with these data, our investigation confirmed that introducing immunotherapy within the peri-dCRT window resulted in a 2-year OS of 66.9%, a figure above the 56.5% 2-year OS observed with dCRT alone in the historical reference set.

On the other hand, a contemporary phase II prospective trial (EC-CRT-001) that enrolled 42 participants failed to demonstrate a survival advantage from combining immunotherapy with dCRT. The survival curves in that trial suggested a 2-year OS of around 50%, which was lower than the rates observed in our study and in our historical control arm [14]. One possible explanation could lie in the heavier burden of T3–4 (71% vs. 59.7%) and N2–3 (81% vs. 63.4%) disease within the EC-CRT-001 cohort. Additionally, because follow-up in that trial extended to a median of merely 14.9 months, the 2-year OS figure will need recalibration once longer follow-up maturity is achieved.

Published literature suggests that after dCRT for ESCC, the proportion of patients experiencing locoregional relapse ranges from 42.9% to 50.7%, whereas the distant metastasis rate ranges from 27.5% to 48.0% [23-25]. A handful of dCRT+ICI reports have specifically dissected post-treatment recurrence patterns. For example, Park *et al*. [13] analysis revealed that the dCRT+ICI arm showed reductions in both locoregional failure (20% vs. 33.3%) and distant metastatic events (15.0% vs. 45.3%) compared with the dCRT-only arm. In the current cohort, 32.0% of individuals developed locoregional progression, and 22.4% manifested distant metastases. Regrettably, we were unable to perform a matched locoregional recurrence comparison because progression details were unavailable for our historical control group. Moreover, it is worth noting that both our study and Park *et al*. [13] investigation have median surveillance periods that fall short of the 3-year mark. Accordingly, subsequent efforts should incorporate longer observation windows and expand recruitment numbers to substantiate our findings and to ascertain whether immunotherapy genuinely reshapes the pattern of disease relapse.

The optimal sequence of immunotherapy alongside radiation remains unclear. The PACIFIC strategy (dCRT followed by durvalumab for stage III NSCLC) laid the foundation for consolidative immunotherapy in unresectable NSCLC [26]. Some evidence suggests that the interval at which concurrent dCRT is delivered may elicit fluctuations in circulating tumor-reactive CD8+ T lymphocytes. Specifically, the abundance of these cells increases during dCRT, peaks in the final week of radiotherapy, and then declines by 1 month after dCRT [27]. Subgroup analyses from the PACIFIC dataset indicate that earlier durvalumab delivery—within a fortnight of completing dCRT—may yield a superior survival benefit compared with later initiation [26]. This observation suggests potential advantages of commencing immunotherapy either concurrently with radiation or during early consolidation [27]. Among our consolidation cohort, the median delay from the final radiation fraction to immunotherapy initiation was 44 days, and this group had worse PFS than the induction and concurrent immunotherapy groups. Such patterns echo earlier findings and further suggest that delaying immunotherapy beyond the completion of radiotherapy risks blunting synergy. Having said that, the limited number of subjects in our consolidation arm constrains the weight of these conclusions.

Radiotherapy target volumes for esophageal cancer routinely cover a substantial length of the primary tumor together with draining nodal stations encompassing the supraclavicular, mediastinal, and abdominal territories. Prolonged exposure of a broad field to moderate radiation doses can compromise immune integrity by depleting effector cells indispensable for mounting effective antitumor immunity [28]. In addition, superimposing ICIs onto concurrent dCRT may heighten toxicity. This could shed light on why the PACIFIC-2 study, which assessed concurrent and consolidative durvalumab alongside dCRT for stage III NSCLC, failed to demonstrate a survival benefit over dCRT alone [15]. For esophageal cancer specifically, randomized phase III data that would firmly establish the correct sequence of immunotherapy with radiotherapy are still awaited. Drawing on our observations, induction chemoimmunotherapy may well represent the preferred approach, as tumor downsizing following induction therapy can permit contraction of radiation target volumes, afford superior shielding of organs at risk, and reduce lymphocyte attrition. In addition, Ai *et al*. [17] demonstrated that induction chemoimmunotherapy can

promote vascular normalization and reduce hypoxia in esophageal tumors, thereby augmenting radiosensitivity and improving prognosis. These observations suggest that early immunotherapy, administered well before radiation, may confer greater survival benefits in inoperable LA-ESCC. In our dataset, the PFS superiority over the consolidation arm endured in the induction arm after sIPTW balancing, further buttressing the case for induction immunotherapy for this patient population. While the signs at present favor induction chemoimmunotherapy over alternative sequences, prospective randomized trials are still required to definitively determine the optimal sequencing of immunotherapy combined with radiotherapy in esophageal cancer.

In the present investigation, any-grade TRAE rates for esophagitis and pneumonitis across the full cohort were 74.8% and 15.1%, respectively, with grade 3–4 occurrences at 12.6% and 5.9%, respectively. In the report by Zhang *et al*. [12], the frequencies of esophagitis and pneumonitis rated at grade 3 or higher were 20% and 4%, respectively, whereas the EC-CRT-001 trial documented corresponding figures of 10% and 6.1%, respectively [14]. These numbers align closely with our own observations. Our data further revealed that grade 3–4 leukopenia and neutropenia were considerably more prevalent within the induction arm (25.9% and 20.4%, respectively) than in the concurrent arm (12.3% and 3.5%) or the consolidation arm (0% and 0%). Such a pattern may reflect pronounced myelosuppression coupled with depleted hematopoietic reserve following induction treatment. In addition, we noted a markedly higher incidence of esophagitis and pneumonitis in the concurrent arm—22.8% and 8.8%, respectively—relative to the induction arm (3.7% and 3.7%) and the consolidation arm (0% and 0%). This observation is plausibly driven by additive toxicity from overlapping treatment administrations.

Certain shortcomings of this study deserve acknowledgment. To begin with, its retrospective design may have introduced inherent selection bias into the data-collection approach. Missing data points also constrain the interpretation of results. Other drawbacks include the absence of uniform target volume delineation and heterogeneity in both chemotherapy backbones and PD-1 agent manufacturers. Additionally, the consolidation immunotherapy subgroup had fewer cases than the other two timing arms. A final limitation is the unavailability of PD-L1 expression results, which prevented exploration of any link between PD-L1 status and survival. That said, several large-scale randomized controlled trials in advanced ESCC have demonstrated comparable efficacy gains with immune-based combination therapy across PD-L1 expression subgroups [11, 29, 30]. At present, routine PD-L1 testing before immunotherapy is not standard practice for ESCC patients in China.

Taken together, the evidence from this study indicates that integrating immunotherapy with dCRT confers encouraging efficacy and an acceptable safety profile in patients with inoperable ESCC. Regarding the order of treatment components, early introduction of immunotherapy—either before or during radiotherapy—was associated with superior PFS.

Acknowledgments: Xiongtao Yang, Xiaomin Wang, Qin Xiao, Xiaolin Ge: Conceptualization, Methodology, Data Curation, Writing-Original Draft.

Nuo Yu, Jiao Li, Ziyu Zheng, Guojie Feng, Yingying Jiang, Lin Lu, Xiaojie Xia, Lei Deng, Tao Zhang, Wenqing Wang, Wenyang Liu, Jianyang Wang, Zefen Xiao, Zongmei Zhou, Nan Bi: Data Collection.

Hui Wang, Cheng Chen: Data Collection, Writing-Review & Editing.

Xin Wang: Conceptualization, Methodology, Writing-Review & Editing, Funding Acquisition, Literature Review.

Conflict of Interest: None

Financial Support: None

Ethics Statement: This study involving human participants was reviewed and approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee, and with the 1964 Declaration of Helsinki and its later amendments (or comparable ethical standards). The ethical approval number was not provided because the study was exempt from formal approval as it involved only anonymized retrospective data. Informed consent was waived, considering the retrospective nature of the study. The trial is registered with ClinicalTrials.gov (Trial no. NCT04821778).

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.
2. Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J, et al. The global landscape of esophageal squamous cell carcinoma and esophageal adenocarcinoma incidence and mortality in 2020 and projections to 2040: new estimates from GLOBOCAN 2020. Gastroenterology. 2022;163(3):649-58.e2.
3. Herskovic A, Martz K, Al-Sarraf M, Herskovic A, Leichman L, Brindle J, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326(24):1593-8.
4. Minsky BD, Pajak TF, Ginsberg RJ, Pisansky TM, Martenson J, Komaki R, et al. INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol. 2002;20(5):1167-74.
5. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). JAMA. 1999;281(17):1623-7.
6. Wang X, Liang F, Wang X, Wu Y, Wang D, Cheng Y, et al. Quality of life and survival outcomes of patients with inoperable esophageal squamous cell carcinoma after definitive radiation therapy: a multicenter retrospective observational study in China from 2015 to 2016. J Natl Cancer Cent. 2023;3(2):150-8.
7. Chen Y, Ye J, Zhu Z, Zhao W, Zhou J, Wu C, et al. Comparing paclitaxel plus fluorouracil versus cisplatin plus fluorouracil in chemoradiotherapy for locally advanced esophageal squamous cell cancer: a randomized, multicenter, phase III clinical trial. J Clin Oncol. 2019;37(20):1695-703.
8. Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. N Engl J Med. 2022;386(5):449-62.
9. Sun JM, Shen L, Shah MA, Enzinger P, Adenis A, Doi T, et al. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet. 2021;398(10302):759-71.
10. Luo H, Lu J, Bai Y, Mao T, Wang J, Fan Q, et al. Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: the ESCORT-1st randomized clinical trial. JAMA. 2021;326(10):916-25.
11. Wang ZX, Cui C, Yao J, Zhang Y, Li M, Feng J, et al. Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): a multicenter phase 3 trial. Cancer Cell. 2022;40(3):277-88.e3.
12. Zhang W, Yan C, Zhang T, Chen X, Dong J, Zhao J, et al. Addition of camrelizumab to docetaxel, cisplatin, and radiation therapy in patients with locally advanced esophageal squamous cell carcinoma: a phase 1b study. Oncoimmunology. 2021;10(1):1971418.
13. Park S, Oh D, Choi YL, Chi SA, Kim K, Ahn MJ, et al. Durvalumab and tremelimumab with definitive chemoradiotherapy for locally advanced esophageal squamous cell carcinoma. Cancer. 2022;128(11):2148-58.
14. Zhu Y, Wen J, Li Q, Chen B, Zhao L, Liu S, et al. Toripalimab combined with definitive chemoradiotherapy in locally advanced oesophageal squamous cell carcinoma (EC-CRT-001): a single-arm, phase 2 trial. Lancet Oncol. 2023;24(4):371-82.
15. Bradley JD, Nishio M, Okamoto I, Newton MD, Trani L, Shire NJ, et al. PACIFIC-2: phase 3 study of concurrent durvalumab and platinum-based chemoradiotherapy in patients with unresectable stage III NSCLC. J Clin Oncol. 2019;37(15 Suppl):TPS8573.
16. Samstein R, Rimner A, Chaft JE, Yamada Y. Combined immune checkpoint blockade and radiation therapy: timing and dose fractionation associated with greatest survival duration among over 750 treated patients. Int J Radiat Oncol Biol Phys. 2017;99(2 Suppl):S129-30.
17. Ai D, Hao S, Shen W, Wu Q, Zhang S, Chen Y, et al. Induction sintilimab and chemotherapy followed by concurrent chemoradiotherapy for locally advanced esophageal cancer: a proof-of-concept, single-arm, multicenter, phase 2 trial. EClinicalMedicine. 2024;69:102471.

18. Yu R, Wang W, Li T, Li J, Zhao K, Wang W, et al. RATIONALE 311: tislelizumab plus concurrent chemoradiotherapy for localized esophageal squamous cell carcinoma. Future Oncol. 2021;17(31):4081-9.
19. Shah MA, Bennouna J, Doi T, Shen L, Kato K, Adenis A, et al. KEYNOTE-975 study design: a phase III study of definitive chemoradiotherapy plus pembrolizumab in patients with esophageal carcinoma. Future Oncol. 2021;17(10):1143-53.
20. Wang L, Chen M, Kato K, Wyrwicz L, Smyth EC, Jiang A, et al. A phase 3 randomized, double-blind, placebo-controlled, multicenter, global study of durvalumab with and after chemoradiotherapy in patients with locally advanced, unresectable esophageal squamous cell carcinoma: KUNLUN. J Clin Oncol. 2022;40(4 Suppl):TPS373.
21. Goodman KA, Xu RH, Chau I, Chen MH, Cho BC, Shah MA, et al. SKYSCRAPER-07: a phase III, randomized, double-blind, placebo-controlled study of atezolizumab with or without tiragolumab in patients with unresectable ESCC who have not progressed following definitive concurrent chemoradiotherapy. J Clin Oncol. 2022;40(4 Suppl):TPS374.
22. Kishan AU, Cook RR, Ciezki JP, Ross AE, Pomerantz MM, Nguyen PL, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in patients with Gleason score 9-10 prostate cancer. JAMA. 2018;319(9):896-905.
23. Welsh J, Settle SH, Amini A, Xiao L, Suzuki A, Hayashi Y, et al. Failure patterns in patients with esophageal cancer treated with definitive chemoradiation. Cancer. 2012;118(10):2632-40.
24. Sudo K, Xiao L, Wadhwa R, Shiozaki H, Elimova E, Taketa T, et al. Importance of surveillance and success of salvage strategies after definitive chemoradiation in patients with esophageal cancer. J Clin Oncol. 2014;32(30):3400-5.
25. Xi M, Xu C, Liao Z, Hofstetter WL, Blum Murphy M, Maru DM, et al. The impact of histology on recurrence patterns in esophageal cancer treated with definitive chemoradiotherapy. Radiother Oncol. 2017;124(2):318-24.
26. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med. 2018;379(24):2342-50.
27. Kim KH, Pyo H, Lee H, Oh D, Noh JM, Ahn YC, et al. Dynamics of circulating immune cells during chemoradiotherapy in patients with non-small cell lung cancer support earlier administration of anti-PD-1/PD-L1 therapy. Int J Radiat Oncol Biol Phys. 2022;113(2):415-25.
28. Filatenkov A, Baker J, Mueller AM, Kenkel J, Ahn GO, Dutt S, et al. Ablative tumor radiation can change the tumor immune cell microenvironment to induce durable complete remissions. Clin Cancer Res. 2015;21(16):3727-39.
29. Lu Z, Wang J, Shu Y, Liu L, Kong L, Yang L, et al. Sintilimab versus placebo in combination with chemotherapy as first-line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): multicentre, randomised, double-blind, phase 3 trial. BMJ. 2022;377:e068714.
30. Xu J, Kato K, Raymond E, Hubner RA, Shu Y, Pan Y, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2023;24(5):483-95.