

Research Article

The Neoadjuvant Administration of PD-1 Inhibitor plus Concurrent Chemoradiotherapy in Patients with Locally Advanced Esophageal Squamous-Cell Carcinoma

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Objective. Programmed cell death-1 (PD-1) inhibitors have shown potency for neoadjuvant therapy in several cancers, while their administration combined with concurrent chemoradiotherapy (CCRT) as a neoadjuvant therapy for locally advanced esophageal squamous-cell carcinoma (ESCC) is seldom reported. The current study aimed to investigate the pathological response, survival, and safety of neoadjuvant PD-1 inhibitor plus CCRT in locally advanced ESCC patients. **Methods.** Twenty-five locally advanced ESCC patients who underwent PD-1 inhibitor plus CCRT neoadjuvant therapy were retrospectively reviewed. Data regarding radiological response, pathological response, disease-free survival (DFS), overall survival (OS), and adverse events were retrieved. **Results.** Two (8.0%), 14 (56.0%), 9 (36.0%), and 0 (0.0%) patients had a clinical response of complete response, partial response, stable disease, and progressive disease after neoadjuvant therapy by radiological evaluations, respectively. Notably, 25 (100.0%) patients had successful tumor resections, 24 (96.0%) patients realized R0 resection, and 13 (52.0%) patients achieved pathological complete response (pCR) by pathological evaluations. Regarding survival profiles, the 1-year and 2-year accumulating DFS rates were 90.0% and 74.6%, respectively; then, the 1-year and 2-year accumulating OS rates were 95.5% and 90.4%, respectively. The top prevalent adverse events were fatigue (48.0%), nausea and vomiting (40.0%), leukopenia (36.0%), neutropenia (36.0%), and peripheral neuropathy (36.0%). In addition, grades 3-4 adverse events included peripheral neuropathy (12.0%), nausea and vomiting (4.0%), leukopenia (4.0%), neutropenia (4.0%), anemia (4.0%), and pruritus (4.0%). **Conclusion.** Neoadjuvant PD-1 inhibitor plus CCRT shows a good efficacy and acceptable tolerance for locally advanced ESCC treatment, but further large-scale study validation is needed.

1. Introduction

Esophageal carcinoma ranks as the seventh most prevalent cancer and the sixth leading cause of cancer-related deaths worldwide according to the most recent Global Cancer Statistics Report [1], among which esophageal squamous-cell carcinoma (ESCC) accounts for the majority [2, 3]. Regarding early stage ESCC patients with less invasion, tumor resection is the primary choice for curative treatment [4]; however, for most cases, ESCC is diagnosed at an advanced stage that loses the chance for curative resection, leading to worse outcomes [5]. Fortunately, the introduction

of neoadjuvant therapy increases the opportunity for tumor resection and improves the long-term prognosis in some advanced ESCC patients, such as locally advanced ESCC patients [6, 7].

Programmed cell death-1 (PD-1) inhibitor is a milestone in cancer immunotherapy and has been largely applied and has greatly improved the prognosis of various cancers [8–11]. In terms of ESCC, several studies have suggested an encouraging benefit of PD-1 inhibitor administration in advanced diseases [12, 13]. In addition, some recent trials uncovered the potency of PD-1 inhibitor plus chemotherapy as a neoadjuvant regimen for locally advanced ESCC

treatment [14–16]. For instance, a recent study revealed that neoadjuvant PD-1 inhibitor plus chemotherapy achieves a 96.3% R0 resection rate and a 33.3% pathological complete response (pCR) rate in locally advanced ESCC patients [14]; another trial showed that PD-1 inhibitor plus chemotherapy as neoadjuvant administration achieves a 100.0% R0 resection rate and 36.0% pCR rate in locally advanced ESCC patients [15]. However, the administration of neoadjuvant PD-1 inhibitor plus concurrent chemoradiotherapy (CCRT) for locally advanced ESCC has seldom been investigated.

Therefore, the current study aimed to explore the pathological response, survival, and safety profiles of neoadjuvant PD-1 inhibitor plus CCRT in locally advanced ESCC patients.

2. Methods

2.1. Patients. This research reviewed twenty-five locally advanced ESCC patients who received PD-1 inhibitor plus CCRT as neoadjuvant therapy in our hospitals from January 2020 to March 2022. The screening criteria were as follows: (a) patients were diagnosed with ESCC by gastroscopy and pathological examination; (b) patients were above 18 years old; (c) patients were confirmed to have locally advanced ESCC with stages of T1b-3/N1-3/M0 or T3/N0/M0 based on the 8th UICC-TNM classification [17]; and (d) patients received a PD-1 inhibitor plus CCRT as neoadjuvant therapy. Patients who did not have follow-up information after tumor resection or who did not consent to the use of their data in this study by themselves or their guardians were ineligible for inclusion. The Ethics Committee of Lishui City People's Hospital offered approval, and the enrolled patients or their guardians offered informed consent.

2.2. Treatment. The patients received PD-1 inhibitor plus CCRT as neoadjuvant therapy for 6 weeks (2 cycles of PD-1 inhibitor, 5 weeks of continuous weekly chemoradiotherapy), followed by tumor resection based on the reassessment of resectability after 4–6 weeks of neoadjuvant therapy. The PD-1 inhibitors included camrelizumab, sintilimab, and others. The chemotherapy regimen involved (a) paclitaxel + cisplatin and (b) paclitaxel + carboplatin. The details of the regimens were described in previous studies [18–20]. The total radiation dosages were 41.4 Gy in 23 fractions (41.4 Gy/23 F) or 40.0 Gy in 20 fractions (40 Gy/20 F) for 5 days per week [18].

2.3. Data Collection. Demographics, disease-related data, and treatment information were collected. Additionally, the results of imaging examinations were obtained, and then the clinical response was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) [21]. Based on surgery information, the R0 resection rate was measured. In addition, the pathological response was assessed via the tumor regression grade (TRG) system, which was categorized as TRG1, 0% vital residual tumor cells; TRG2, <10% vital residual tumor cells; TRG3, 10%–50% vital residual tumor cells; and TRG4, >50% vital residual tumor cells [20]. Patients who were classified as

TRG1 were considered to have a pathological complete response (pCR). Meanwhile, pathologic tumor-node-metastasis stage post neoadjuvant therapy (ypTNM stage) was evaluated. Furthermore, the follow-up information of patients was obtained, based on which disease-free survival (DFS) and overall survival (OS) were imputed. DFS was defined as the duration from surgery to disease relapse or death; OS was defined as the duration from neoadjuvant therapy to death. For safety analysis, adverse events were counted and graded via the Common Terminology Criteria for Adverse Events (CTCAE, v4.0, available at <https://ctep.cancer.gov>).

2.4. Statistics. SPSS v22.0 (IBM Corp., USA) was adopted for analysis, and GraphPad Prism v8.0 (GraphPad Software, Inc., USA) was adopted for plotting. Continuous data were checked for normality by the Kolmogorov–Smirnov test, and then normally distributed continuous variables were expressed as mean ± standard deviation (SD). The categorized variables were expressed as counts (percentage). DFS and OS were elucidated using Kaplan–Meier curves, and then 1-year and 2-year accumulating DFS and OS rates were calculated as percentages. The comparisons of categorized variables between two groups or among three (or above) groups were performed via the chi-square test or Fisher's exact test as appropriate. The comparisons of DFS and OS between two groups or among three groups were performed via log-rank test. $P < 0.05$ represented statistical significance.

3. Results

3.1. Patient Characteristics. Twenty-five locally advanced ESCC patients were analyzed in the current study, with a mean age of 59.7 ± 7.8 years (Table 1). Two (8.0%) and 23 (92.0%) patients had a clinical stage of cT2 and cT3, respectively; meanwhile, 16 (64.0%), 7 (28.0%), and 2 (8.0%) patients had a clinical stage of cN1, cN2, and cN3, respectively. Meanwhile, 13 (52.0%), 8 (32.0%), and 4 (16.0%) ESCC patients had PD-L1 CPSs (%) of 1–4, 5–9, and ≥ 10 , respectively. Detailed information on other patient characteristics and treatment regimens is listed in Table 1.

3.2. Treatment Response. After neoadjuvant therapy, 2 (8.0%), 14 (56.0%), 9 (36.0%), and 0 (0.0%) patients had a clinical response of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively, by radiological evaluation (Table 2). Meanwhile, the objective response rate (ORR) was 64.0%.

Twenty-five (100.0%) patients had successful tumor resections, and 24 (96.0%) patients achieved R0 resection. By pathological evaluation, 13 (52.0%), 5 (20.0%), 6 (24.0%), and 1 (4.0%) patients had TRG1, TRG2, TRG3, and TRG4, respectively. Importantly, 13 (52.0%) patients achieved pCR (Table 3).

In addition, 13 (52.0%), 1 (4.0%), 1 (4.0%), 1 (4.0%), 2 (8.0%), 3 (12.0%), and 4 (16.0%) patients were evaluated as ypT0N0M0, ypT0N1M0, ypT1bN1M0, ypT1bN3M0, ypT2N0M0, ypT3N0M0, and ypT3N2M0, respectively, by pathological confirmations after neoadjuvant therapy (Table 4).

TABLE 1: Clinical characteristics of locally advanced ESCC patients.

Characteristics	Locally advanced ESCC patients (N = 25)
Age (years), mean ± SD	59.7 ± 7.8
Gender, no. (%)	
Female	7 (28.0)
Male	18 (72.0)
Tumor location, no. (%)	
Upper	1 (4.0)
Middle	19 (76.0)
Lower	5 (20.0)
Histological type, no. (%)	
ESCC	25 (100.0)
cT stage, no. (%)	
cT2	2 (8.0)
cT3	23 (92.0)
cN stage, no. (%)	
cN1	16 (64.0)
cN2	7 (28.0)
cN3	2 (8.0)
cM, no. (%)	
cM0	25 (100.0)
cTNM, no. (%)	
III	23 (92.0)
IVA	2 (8.0)
PD-1 regimen, no. (%)	
Camrelizumab	12 (48.0)
Sintilimab	8 (32.0)
Others	5 (20.0)
Chemotherapy regimen, no. (%)	
Paclitaxel + cisplatin	11 (44.0)
Paclitaxel + carboplatin	14 (56.0)
RT dose, no. (%)	
40 Gy/20 F	13 (52.0)
41.4 Gy/23 F	12 (48.0)
PD-L1 CPS, no. (%)	
0	0 (0.0)
1–4	13 (52.0)
5–9	8 (32.0)
≥10	4 (16.0)

ESCC, esophageal squamous-cell carcinoma; SD, standard deviation; cT, clinical tumor; cN, clinical node; cM, clinical metastasis; cTNM, clinical tumor-node-metastasis; PD-1, programmed cell death protein 1; RT, radiotherapy; 40 Gy/20 F, 40.0 Gy in 20 fractions; 41.4 Gy/23 F, 41.4 Gy in 23 fractions; PD-L1 CPS, programmed death ligand 1 combined positive score.

3.3. Survival Profile. During a median follow-up of 23.3 months (range: 8.4–29.6 months), the 1-year and 2-year accumulating DFS rates were 90.0% and 74.6%, respectively (Figure 1(a)); then, the 1-year and 2-year accumulating OS rates were 95.5% and 90.4%, respectively (Figure 1(b)).

Then, the correlation of ESCC clinical stage with DFS and OS was analyzed (Figures 2(a)–2(f)). It was observed that higher cN stage showed a trend to relate to DFS ($P = 0.142$) and OS ($P = 0.065$), but without statistical significance, which might result from the small sample size of neoadjuvant application cases. In addition, cT stage and cTNM stage were not correlated with DFS or OS, which might be because only 2 cases were cT2 and 2 cases were cTNM IVA.

TABLE 2: Clinical response after neoadjuvant treatment.

Items	Locally advanced ESCC patients (N = 25)
<i>Clinical response, no. (%)</i>	
CR	2 (8.0)
PR	14 (56.0)
SD	9 (36.0)
PD	0 (0.0)
<i>ORR, no. (%)</i>	
Yes	16 (64.0)
No	9 (36.0)

ESCC, esophageal squamous-cell carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response.

TABLE 3: Surgical information and pathological response.

Items	Locally advanced ESCC patients (N = 25)
<i>Surgical information, no. (%)</i>	
Tumor resection rate	25 (100.0)
R0 resection rate	24 (96.0)
<i>TRG system, no. (%)</i>	
TRG1	13 (52.0)
TRG2	5 (20.0)
TRG3	6 (24.0)
TRG4	1 (4.0)
<i>pCR, no. (%)</i>	
Yes	13 (52.0)
No	12 (48.0)

ESCC, esophageal squamous-cell carcinoma; TRG, tumor regression grade; pCR, pathological complete response.

TABLE 4: ypTNM stage.

ypTNM stage	Locally advanced ESCC patients (N = 25)
ypT0N0M0, no. (%)	13 (52.0)
ypT0N1M0, no. (%)	1 (4.0)
ypT1bN1M0, no. (%)	1 (4.0)
ypT1bN3M0, no. (%)	1 (4.0)
ypT2N0M0, no. (%)	2 (8.0)
ypT3N0M0, no. (%)	3 (12.0)
ypT3N2M0, no. (%)	4 (16.0)

ypTNM, post neoadjuvant pathologic tumor-node-metastasis; ESCC, esophageal squamous-cell carcinoma.

3.4. Adverse Events. Detailed information on adverse events is exhibited in Table 5. Briefly, the top prevalent adverse events were fatigue (48.0%), nausea and vomiting (40.0%), leukopenia (36.0%), neutropenia (36.0%), and peripheral neuropathy (36.0%). In addition, grades 3–4 adverse events included peripheral neuropathy (12.0%), nausea and vomiting (4.0%), leukopenia (4.0%), neutropenia (4.0%), anemia (4.0%), and pruritus (4.0%).

The correlation between particular combination of treatment and adverse events, between age and adverse events, and between gender and adverse events was subsequently analyzed. It was observed that leukopenia incidence differed among different treatments ($P = 0.030$, 11

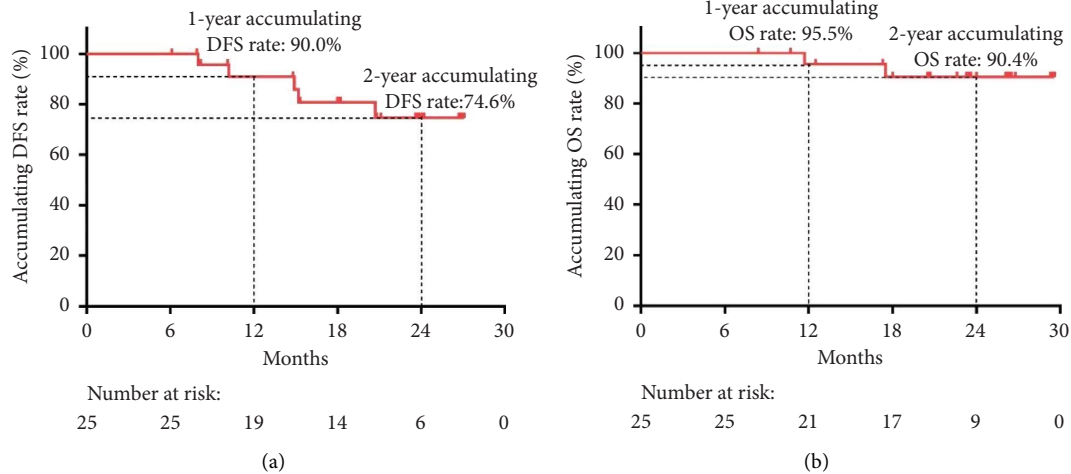


FIGURE 1: Survival data presentation. Information about the accumulating DFS (a) and accumulating OS (b) in the studied patients.

types of combinations in the study), but the incidence of other adverse events did not differ among them (Supplementary Table 1). Meanwhile, no adverse event was related to age or gender (Supplementary Table 2).

4. Discussion

Esophagectomy is considered the main therapy for patients with resectable esophageal cancer and might largely reduce the disease burden of esophageal cancer patients [22]. However, in those patients who are not suitable for receiving esophagectomy directly, such as those with cT2 with a high-risk lesion or cT4, neoadjuvant therapy with platinum-based CCRT is recommended [23]. Unfortunately, the pCR of CCRT alone is not ideal; for instance, the pCR rate is only 26.0% in esophageal cancer patients receiving neoadjuvant CCRT [24]. In another study, the pCR of neoadjuvant CCRT ranged from 16.4% to 16.7% depending on the radiation dose in esophageal cancer patients [25]. The induction of immunotherapy largely elevates the response rate after neoadjuvant therapy; for example, the pCR rate could reach 38% after treating esophageal cancer patients with neoadjuvant immunotherapy combined with CCRT [26]. However, studies on the efficacy of neoadjuvant PD-1 inhibitors and CCRT in locally advanced esophageal cancer patients are less frequently reported. In the current study, it was reported that neoadjuvant PD-1 inhibitors plus CCRT could reach an ORR of 64.0% and a pCR rate of 52.0% in locally advanced esophageal cancer patients. These data were numerically higher than those in a previous study that administered neoadjuvant CCRT monotherapy to esophageal cancer patients. These findings could be explained as follows. (1) PD-1 inhibitor and CCRT both played an antitumor role during neoadjuvant therapy; therefore, their combination could have a better antitumor effect than CCRT administration alone. (2) It has been reported that PD-1 inhibitor combined with CCRT could have a synergistic antitumor effect; hence, their combination had a better efficacy profile [27]. It is an interesting topic to explore the possible synergistic effect of PD-1 inhibitor and

chemoradiotherapy. A recent review summarizes that immunogenic tumor-cell death, anti-angiogenesis, and effector T cell proliferation contribute to the synergistic effect between PD-1 inhibitor and chemotherapy [28]. Besides, another recent review sums up that chemotherapy involves the anticancer immunity activation by releasing immunostimulatory molecules from dying tumor cells and mediating off-target effect of immune cells, which contributes to the enhancement of the antitumor effect of PD-1 inhibitor [29]. Regarding radiotherapy, several recent reviews summarize that radiotherapy not only kills tumor cells directly but also modifies tumor microenvironment to promote the recognition of tumor cells by immune system; meanwhile, it can upregulate tumor-related antigens, stimulate the secretion of cytokines, and induce the proliferation of CD8⁺ T cells, therefore synergizing with PD-1 inhibitor [30, 31].

Apart from the pCR rate, the survival outcome is also of great concern after neoadjuvant therapy in locally advanced esophageal cancer patients. In the CROSS study, neoadjuvant CCRT followed by surgery achieved a median OS of 48.6 months in esophageal or junctional cancer patients [32]. In the NEOCRTEC 5010 study, they reported that the median OS could reach 100.1 months after treating esophageal squamous-cell carcinoma patients with neoadjuvant CCRT [33]. In addition, the 1-year and 2-year OS rates ranged from 81% to 90% and from 67% to 75.1%, respectively, in these two studies [32, 33]. In the present study, limited by the follow-up duration, the median OS was not achieved; the 1-year OS was 90.9%, and the 2-year OS was 74.6%, which were comparable to those in a previous study that applied neoadjuvant CCRT in esophageal cancer patients. The possible reason might be derived from the following. (1) OS might be affected by multiple aspects but not only the pCR rate or the R0 resection rate, and the subsequent adjuvant therapy might also affect the OS; therefore, the OS seemed similar between the results from our study and those from a previous study. (2) Due to the limited application duration of neoadjuvant PD-1 inhibitor plus CCRT in esophageal cancer patients, the follow-up duration was short in this study, which caused the median OS to not

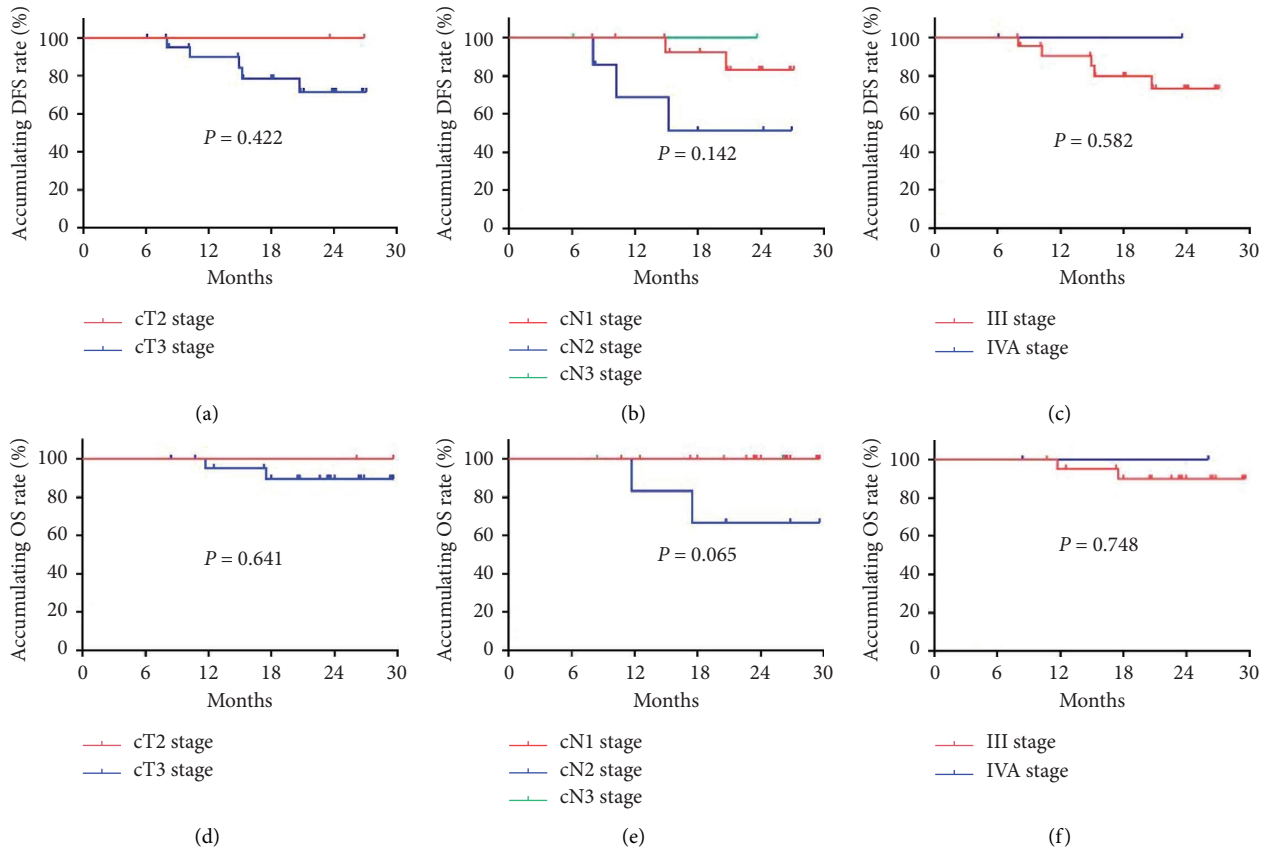


FIGURE 2: Correlation of clinical stage with DFS and OS in the studied patients. The correlation of cT stage (a), cN stage (b), and cTNM stage (c) with DFS. The correlation of cT stage (d), cN stage (e), and cTNM stage (f) with OS.

TABLE 5: Adverse events.

Events	Total, no. (%)	Grade 1-2, no. (%)	Grade 3-4, no. (%)
Fatigue	12 (48.0)	12 (48.0)	0 (0.0)
Nausea and vomiting	10 (40.0)	9 (36.0)	1 (4.0)
Leukopenia	9 (36.0)	8 (32.0)	1 (4.0)
Neutropenia	9 (36.0)	8 (32.0)	1 (4.0)
Peripheral neuropathy	9 (36.0)	6 (24.0)	3 (12.0)
Anemia	8 (32.0)	7 (28.0)	1 (4.0)
Pruritus	8 (32.0)	7 (28.0)	1 (4.0)
Hand-foot syndrome	8 (32.0)	8 (32.0)	0 (0.0)
Elevated transaminase	7 (28.0)	7 (28.0)	0 (0.0)
Diarrhea	5 (20.0)	5 (20.0)	0 (0.0)
Thrombocytopenia	4 (16.0)	4 (16.0)	0 (0.0)
Fever	4 (16.0)	4 (16.0)	0 (0.0)
Anorexia	4 (16.0)	4 (16.0)	0 (0.0)
Hypertension	4 (16.0)	4 (16.0)	0 (0.0)
Elevated bilirubin	3 (12.0)	3 (12.0)	0 (0.0)

be achieved in this study. Therefore, further study with a more extended follow-up period is needed.

Safety concerns are noteworthy during the administration of the PD-1 inhibitor and CCRT. In a previous study, it was shown that the most common adverse events during PD-1 inhibitor administration are hematological adverse events, such as anemia and leukopenia, and chemoradiation-related adverse events, including fatigue, nausea, and vomiting [34–36]. Furthermore, a previous trial reports that

the most common adverse events of neoadjuvant CCRT in esophageal cancer patients are leukopenia, neutropenia, anemia, vomiting, and thrombocytopenia [37]. Similar to these previous studies, the most common adverse events of neoadjuvant PD-1 inhibitor and CCRT in esophageal cancer patients of this study included fatigue (48.0%), nausea and vomiting (40.0%), leukopenia (36.0%), neutropenia (36.0%), peripheral neuropathy (36.0%), and anemia (32.0%). These findings indicated that the safety profile of neoadjuvant PD-

1 inhibitor plus CCRT was acceptable in esophageal cancer patients, and no new adverse events occurred.

Some limitations were nonnegligible. (1) This was a single-arm study, and the lack of a control group was the main limitation. (2) This study had a short follow-up duration; therefore, it was challenging to draw solid conclusions about the long-term efficacy and safety of the treatment regimen, leading to the conclusion that a further study with a longer follow-up period is needed. (3) The sample size of this study was relatively small, limiting the generalizability of the findings and making it hard to further perform post-hoc analyses.

In conclusion, neoadjuvant therapy using PD-1 inhibitor plus CCRT is a potential choice exhibiting good efficacy and acceptable tolerance for locally advanced ESCC treatment. However, further large-scale study validations with longer follow-up duration are needed.

Data Availability

All data supporting the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary Table 1: correlation of any particular combination of treatment with adverse events. Supplementary Table 2: correlation of age and gender with adverse events. (*Supplementary Materials*)

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