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ORIGINAL RESEARCH

The Safety and Efficacy of Neoadjuvant Camrelizumab Plus Chemotherapy in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma: A Retrospective Study

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Background: Neoadjuvant anti-programmed death receptor-1 (PD-1) blockade has been explored in the treatment of locally advanced esophageal squamous cell carcinoma (ESCC). We conducted this study to assess the efficacy and safety of neoadjuvant camrelizumab plus chemotherapy in locally advanced ESCC.

Methods: We retrospectively enrolled ESCC patients who received surgery within 3 months of treatment with camrelizumab plus chemotherapy from June 2019 to January 2021.

Results: A total of 34 eligible patients were enrolled. The neoadjuvant treatment was well tolerated with no serious treatment-related adverse events. Thirty-two (94.1%) patients achieved a R0 resection, and 14 patients (41.2%) developed postoperative complications. The objective response rate (ORR) was 61.8% and the disease control rate (DCR) was 100.0%. The major pathological response (MPR), pathological complete response (pCR), and clinical to pathological downstaging rate were 50.0%, 35.3%, and 79.4%, respectively. With a median follow-up of 14.8 months, 30 (88.2%) patients who underwent surgical resection remain alive. The disease-free survival (DFS) and overall survival (OS) at 12 months were 86.4% and 92.8%, respectively.

Conclusion: Neoadjuvant camrelizumab plus chemotherapy is safe and efficacious in treating patients with locally advanced ESCC.

Keywords: esophageal squamous cell carcinoma, neoadjuvant therapy, camrelizumab, chemotherapy, survival

Introduction

Esophageal carcinoma is the seventh most common cancer and the sixth leading cause of cancer death worldwide, with over 604,000 newly diagnosed cases and 544,000 annual deaths in 2020.[1] Esophageal squamous cell carcinoma (ESCC) is the predominant histologic subtype, accounting for 87% of all esophageal cancers.[2] Surgery remains as the mainstay treatment for patients with early-stage ESCC; however, a great proportion of patients have developed into locally advanced stage, and surgery alone is not satisfactory due to high recurrence and metastasis rate.[3] With the emergence of neoadjuvant therapy, surgery after neoadjuvant chemoradiotherapy or chemotherapy has progressively emerged as a standard treatment in locally advanced ESCC based on several clinical trials.[4–6] However, the limited survival benefits and increased risk of perioperative toxicities have made it less appealing in clinical practice.[7]

Recently, anti-programmed death receptor-1 (PD-1) agents (nivolumab or pembrolizumab) have been approved by the Food and Drug Administration as second-line treatment in advanced ESCC patients.[8,9] Neoadjuvant anti-PD-1 agents prior to surgery have demonstrated encouraging efficacy with favorable tolerability in several cancers including lung cancer, melanoma and colorectal cancer.[10–12] Moreover, anti-PD-1 agents combined with chemotherapy or chemoradiation was recently explored for neoadjuvant therapy in locally advanced ESCC, which exhibited an acceptable therapeutic response and a low-toxicity profile.[13–16] Park et al reported that neoadjuvant pembrolizumab plus platinum-based

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chemoradiotherapy may not increase the operative risk or reduce the quality of radical dissection including lymphadenectomy.[17]

The Phase 3 ESCORT study undertaken in China showed that camrelizumab, a novel IgG4-kappa PD-1 inhibitor, significantly improved overall survival of patients with advanced or metastatic ESCC compared with chemotherapy.[18] However, the report of neoadjuvant camrelizumab plus chemotherapy in treating locally advanced ESCC is limited. In this retrospective study, we aimed to evaluate the efficacy and safety of neoadjuvant camrelizumab plus chemotherapy prior to surgery for patients with locally advanced ESCC.

Materials and Methods

Patient Selection

From June 2019 to January 2021, we retrospectively recruited ESCC patients who underwent surgery within 3 months of treatment with camrelizumab plus chemotherapy at the Zibo Central Hospital (Shandong, China). All patients were histologically confirmed locally advanced ESCC, which was defined as cT1N1-3M0 or cT2-4aN0-3M0 (AJCC, 8th Edition) based on contrast-enhanced computerized tomography (CT), and/or magnetic resonance imaging (MRI), upper gastrointestinal endoscopic ultrasonography (EUS), and cervical lymph node ultrasonography. Patients were aged 18 years or older, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had adequate organ function for surgical resection. Patients were excluded when they had other anti-tumor treatments before or during the neoadjuvant treatment and other significant concurrent malignant tumors. The study was approved by institutional review board of Zibo Central Hospital, and carried out in accordance with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from all patients.

Neoadjuvant Therapy and Surgical Procedures

Camrelizumab was given 200 mg intravenously every 3 weeks (a cycle). Simultaneously, the paclitaxel was administered intravenously at a dose of 100 mg/m^2 of body-surface area on days 1 and 8, and the carboplatin was administered intravenously at an area under the curve of 5 mg/mL per minute on day 1. The surgery was performed at the surgeon's decision after completion of at least 2 cycles of neoadjuvant therapy. Patients were re-evaluated with contrast-enhanced CT within 1 week before surgery. Standard minimally invasive esophagectomy (MIE) was performed for all patients, and the upper tumor mainly was treated with three-incision McKeown surgery (three fields or two fields). The middle and lower segment tumors with two-incision Ivor-Lewis surgery. Besides, a gastric tube was applied to reconstruct the digestive tract after esophagectomy. The surgical indicators, including operative time, blood loss, blood transfusion, hospital stay, and resection margin were first recorded. The postoperative complications, including pneumonia, chylothorax, pleural effusion, wound infection, and recurrent nerve paralysis, were also recorded. Patients were followed postoperatively with routine CT scans every 3 months in the first year following the treatment, and every 6 months thereafter.

Assessment

The primary outcome was disease-free survival (DFS) and overall survival (OS) at 12 months. DFS was defined as the time from diagnosis until disease recurrence or death, and overall survival defined as the time from diagnosis to date of death. Secondary outcomes were radiologic response prior to surgery, pathological responses including major pathological response (MPR) and pathological complete response (pCR), and treatment-related adverse events (TRAEs). Radiologic responses were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. MPR was defined as residual tumor cells ≤10% at the time of surgery, and pCR was defined as tumors without any viable tumor cells. TRAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Using tumor samples obtained during the surgical resection, tumor cell PD-L1 expression was measured using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, CA, USA). The expression of PD-L1 was defined by the Combined Positive Score (CPS) by dividing the number of PD-L1-stained tumor and immune cells with the total number of viable tumor cells and multiplying by 100: (−) CPS <10, (+) CPS ≥10.[19]

Statistical Analyses

All statistical analyses were done using SPSS 20.0 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were presented with as a mean ± standard deviation or median and range when appropriate, while categorical variables were expressed as counts and percentages. The Kaplan–Meier method was used to estimate DFS and OS and corresponding 95% CIs. Differences were considered to be significant when $P < 0.05$.

Results

Patient Characteristics

A total of 34 eligible patients were included in this study. The baseline characteristics are shown in Table 1. Median age was 59 years (52–69) and most patients were male. Twenty-eight (82.4%) patients had ECOG PS 0 and 6 (17.6%) had ECOG PS 1. Twenty (58.8%) patients were current/ex-smoker. Tumors were located in the proximal third of the esophagus in 4 (11.8%) patients, the middle third in 18 (52.9%) patients, and the distal third in 12 (35.3%) patients. Five (14.7%) patients had stage II, 26 (76.5%) patients had stage III, and 3 (8.8%) had stage IVA. Twenty-three (67.6%) patients had PD-L1 CPS <10 and 9 (26.5%) patients PD-L1 CPS ≥10. Patients received 3 cycles (2–5) of neoadjuvant camrelizumab and chemotherapy before surgery. Time from completion of neoadjuvant therapy to surgery was 23 days (14–38). Moreover, a total of 23 (67.6%)

Table 1 Patient Characteristics

Characteristics	Patients (n = 34)
Age, years	
Median (range)	59 (52–69)
Mean ± SD	60 ± 6.2
Sex	
Male	30 (88.2%)
Female	4 (11.8%)
ECOG PS	
0	28 (82.4%)
1	6 (17.6%)
History of smoking	
Current/ex-smoker	20 (58.8%)
Never-smoker	14 (41.2%)
Tumor location	
Proximal third	4 (11.8%)
Middle third	18 (52.9%)
Distal third	12 (35.3%)
Histologic grade	
Well differentiated	3 (8.8%)
Moderately differentiated	17 (50.0%)
Poorly differentiated	14 (41.2%)
Clinical T stage	
T1	0
T2	4 (11.8%)
T3	27 (79.4%)
T4a	3 (8.8%)
Clinical N stage	
N0	3 (8.8%)
N1	18 (52.9%)
N2	12 (35.3%)
N3	1 (2.9%)

(*Continued*)

Table 1 (Continued).

Characteristics	Patients (n = 34)
Clinical TNM stage (AJCC, 8th edition)	
II	5 (14.7%)
III	26 (76.5%)
IVA	3 (8.8%)
PD-L1 CPS	
<10	23 (67.6%)
≥10	9 (26.5%)
Unevaluable	2 (5.9%)
Cycles of NACI before resection, median (range)	3 (2–5)
Time from completion of NACI to surgery, median (range), days	23 (14–38)
Adjuvant therapy (at least 1 cycle)	23 (67.6%)
Camrelizumab alone	10 (29.4%)
Chemotherapy alone	7 (20.6%)
Camrelizumab plus chemotherapy	6 (17.6%)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; AJCC, American Joint Committee on Cancer; PD-L1, programmed death-ligand 1; CPS, combined positive score; NACI, neoadjuvant chemotherapy combined with immunotherapy;

patients received adjuvant treatments, including 10 (29.4%) receiving camrelizumab alone, 7 (20.6%) receiving chemotherapy alone, and 6 (17.6%) receiving camrelizumab plus chemotherapy.

Safety

The TRAEs during neoadjuvant treatment are shown in Table 2. The most common treatment-related grade 1 or 2 AEs were reactive capillary hemangioma (10 [29.4%]), anemia (4 [11.7%]), decreased appetite (4 [11.7%]), diarrhea (4 [11.7%]), leukopenia (3 [8.8%]), and thrombocytopenia (3 [8.8%]). The most common treatment-related grade 3 or worse AEs included reactive capillary hemangioma (2 [5.9%]), leukopenia (1 [2.9%]), and fatigue (1 [2.9%]). No treatment-related deaths were reported.

Table 2 Treatment-Related Adverse Events During Neoadjuvant Treatment (n = 34)

	Grade 1–2	Grade 3	Grade 4
Anemia	4 (11.7%)	–	–
Leukopenia	3 (8.8%)	1 (2.9%)	–
Thrombocytopenia	3 (8.8%)	–	–
Reactive cutaneous capillary endothelial proliferation	10 (29.4%)	2 (5.9%)	–
Nausea or vomiting	3 (8.8%)	–	–
Decreased appetite	4 (11.7%)	–	–
Diarrhea	4 (11.7%)	–	–
Constipation	3 (8.8%)	–	–
ALT/AST increase	2 (5.9%)	–	–
Fatigue	2 (5.9%)	1 (2.9%)	–
Rash	1 (2.9%)	–	–
Pneumonia	1 (2.9%)	–	–
Hypothyroidism	1 (2.9%)	–	–
Hypertension	1 (3.3%)	–	–

Table 3 Surgical Procedures

Characteristics	Patients (n = 34)
Surgery type	
McKewon	14 (41.2%)
Ivor Lewis	20 (58.8%)
Operation time, median (range), min	225 (115–410)
Blood loss, median (range), mL	176 (110–410)
Blood transfusion, yes	1 (2.9%)
Hospital stays, median (range), days	12 (9–18)
Resection margins	
R0	32 (94.1%)
R1	2 (5.9%)
Postoperative complications	
Pneumonia	4 (11.8%)
Chylothorax	3 (8.8%)
Pleural effusion	3 (8.8%)
Wound infection	2 (5.9%)
Recurrent nerve paralysis	2 (5.9%)

Surgical Treatment

The surgical details are presented in Table 3. Fourteen (41.2%) patients had the McKewon surgery and 20 (58.8%) patients had Ivor Lewis surgery. The median operation time was 225 minutes (115–410), the median amount of blood loss was 176 mL (110–410), and the median hospital stay was 12 days (9–18). Thirty-two (94.1%) patients achieved a R0 resection and 2 (5.9%) patients had a R1 resection. During the postoperative periods, 4 (11.8%) patients had pneumonia, 3 (8.8%) had chylothorax, 3 (8.8%) had pleural effusion, 2 (5.9%) had wound infection, and 2 (5.9%) had recurrent nerve paralysis. There was no death in hospital or any other serious intraoperative complications.

Efficacy

The radiologic and pathologic responses are summarized in Table 4. Of all 34 patients, 2 (5.9%) patients had a complete response (CR), 19 (55.9%) patients had a partial response (PR), and 13 (38.2%) had a stable disease (SD). The objective response rate (ORR) was 61.8% and the disease control rate (DCR) was 100.0%. According to postoperative pathological results, 17 (50.0%) patients had a MPR, 12 (35.3%) patients had a pCR, and 5 (14.7%) patients were non-responders. Twenty-seven (79.4%) patients achieved clinical to pathological downstaging. At the time of data cutoff (July 1, 2021),

Table 4 Radiologic and Pathologic Responses

Characteristics	Patients (n = 34)
Radiologic responses	
Complete response (CR)	2 (5.9%)
Partial response (PR)	19 (55.9%)
Stable disease (SD)	13 (38.2%)
Objective response rate (ORR)	21 (61.8%)
Disease control rate (DCR)	34 (100.0%)
Pathologic responses	
Non-responder	5 (14.7%)
Major pathological response (MPR)	17 (50.0%)
Complete pathological response (pCR)	12 (35.3%)
Clinical to pathological down-staging	27 (79.4%)

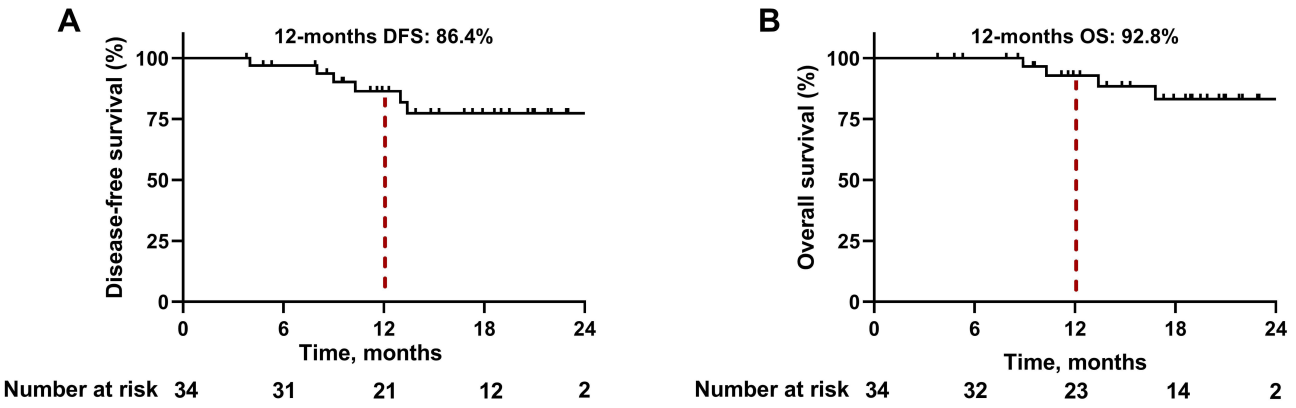

Figure 1 Kaplan–Meier survival curves in all patients. (**A**) Disease-free survival. (**B**) Overall survival.

with a median follow-up of 14.8 months (range 3.8–26.5), 30 (88.2%) of 34 patients were alive and 28 (82.4%) patients remained recurrence-free. Six (17.6%) patients who underwent surgery had recurrence, of whom 4 (11.8%) had died. In the entire patient cohort, the median DFS and OS was not reached (Figure 1). The DFS rate was 86.4% at 12 months, 77.3% at 18 months, and 70.4% at 77.3 months; the OS rate was 92.8% at 12 months, 83.2% at 18 months, and 83.2% at 24 months (Figure 1).

In subgroup analyses regarding pathological response, patients with a MPR or pCR showed better DFS (all $P < 0.001$, Figure 2A) and OS (all $P < 0.001$, Figure 2B) than non-responders. In terms of PD-L1 expression, no significant difference was determined regarding DFS ($P = 0.794$, Figure 3A) and OS ($P = 0.357$, Figure 3B) in patients with PD-L1 CPS <10 or ≥10.

Discussion

This is a retrospective study to assess neoadjuvant camrelizumab plus chemotherapy for locally advanced ESCC patients, which achieved a promising MPR rate of 50.0%, a pCR rate of 35.3%, and the R0 resection rate of 94.1%. This neoadjuvant therapy regimen showed optimal survival outcomes with a DFS of 86.4% and an OS of 92.8% at 12 months. This neoadjuvant treatment was well tolerated with a manageable safety profile.

Previous concern with neoadjuvant treatment remains the delay of surgery due to disease progression or serious TRAEs during neoadjuvant treatment. In our study, no patient progressed during the neoadjuvant treatment duration. Thirteen (38.2%) of 34 patients had multiple level N2-3 disease, which is considered challenging for surgery. Notably, this neoadjuvant therapy obtained a clinical to pathological downstaging rate of 79.4%, which increased the chance of patients with unresectable tumors to have curative surgery. In addition, the surgical procedure was safe and controllable,

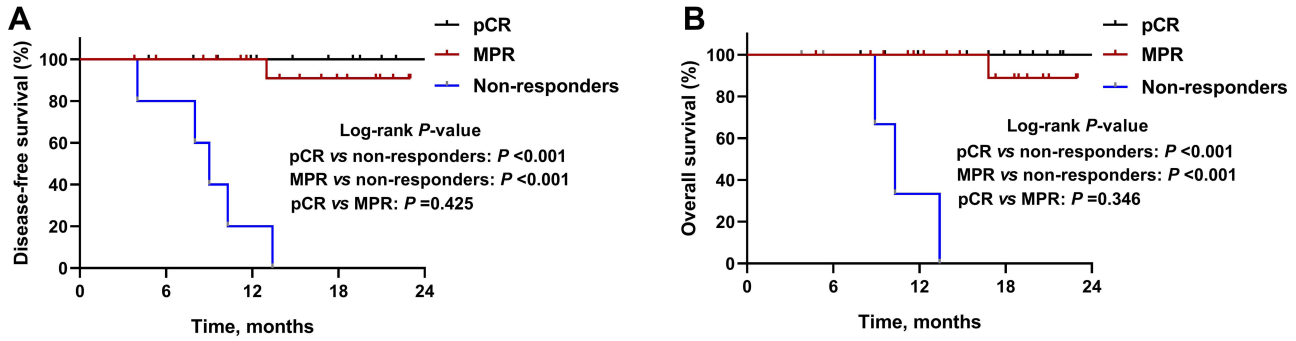

Figure 2 Kaplan–Meier survival curves stratified by pathological responses. (**A**) Disease-free survival and (**B**) overall survival for patients with major pathological response (MPR), complete pathological response (pCR), or non-responders.

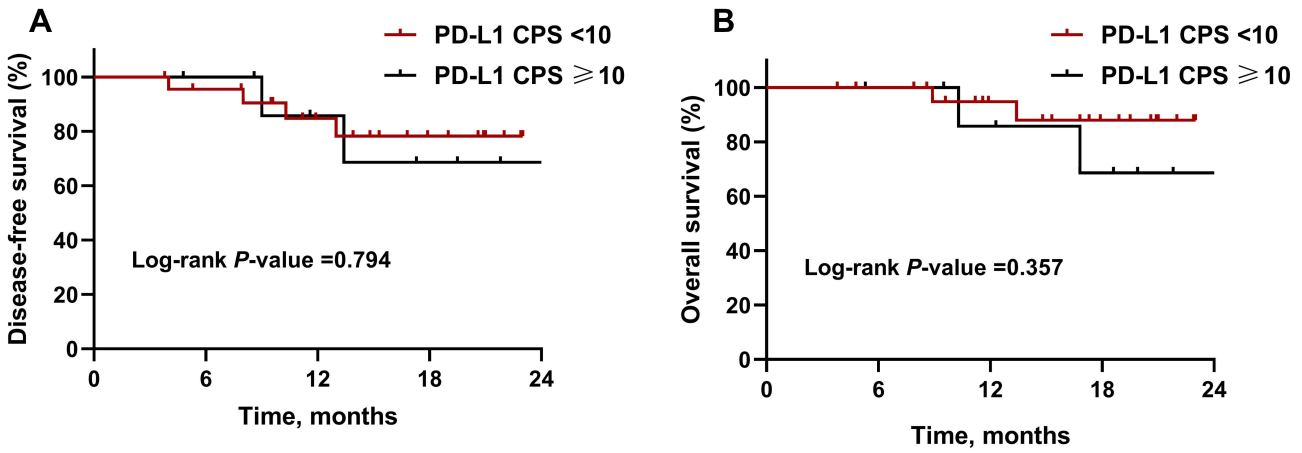

Figure 3 Kaplan–Meier survival curves stratified by PD-L1 expression. (**A**) Disease-free survival and (**B**) overall survival for patients with PD-L1 CPS <10 or ≥10.
Abbreviations: PD-L1, programmed death-ligand 1; CPS, combined positive score.

as blood loss was minimal, operative time and hospital stay were reasonable, and the rate of surgical complications was low. Nearly all patients had R0 resection, which underlines the feasibility and utility of resection in this population.

As to the therapeutic efficacy of neoadjuvant PD-1 blockade and chemotherapy, Shen et al reported an R0 resection rate of 96.3%, a pCR rate of 33.3%, and an ORR of 88.9% in patients with locally advanced ESCC treating neoadjuvant nivolumab or pembrolizumab plus chemotherapy.[14] In one retrospective study evaluating locally advanced ESCC patients receiving neoadjuvant immunotherapy (camrelizumab, pembrolizumab, or sintilimab) plus chemotherapy, the pCR rate was 34.21%, the MPR rate was 42.1%, and the R0 resection rate was 92.11%.[15] Moreover, another retrospective study with 12 cases, which assessed the safety and feasibility of neoadjuvant camrelizumab plus chemotherapy in locally advanced ESCC, reported a pCR rate of 33.3% and a MPR of 41.7%.[13] In another study including 16 cases conducted by Yang et al, the ORR was 81.3%, the DCR was 100%, the pCR rate was 31.3%, and the R0 resection rate was 93.8% in locally advanced ESCC patients receiving neoadjuvant camrelizumab plus chemotherapy.[16] They also reported the survival profile including a 1-year PFS of 83% and OS of 90.9%. In this study, 17 (50.0%) patients had a MPR, 12 (35.3%) patients had a pCR, and the survival was favorable with a DFS of 86.4% and an OS of 92.8% at 12 months. Overall, much more impressive results of pathological responses and survival outcomes were determined in the present study compared with the above studies. Moreover, this study adopted a rather homogenous PD-1 inhibitor regimen (camrelizumab) with a relatively larger number of patients. This neoadjuvant treatment regimen was well tolerated, with most Grade 1–2 AE, only 4 Grade 3 AE, and no Grade 4 AEs. TRAEs were well monitored and managed with toxic effects similar to anti-PD-1 agents or chemotherapy as previously reported.

Subgroup analysis found that pathological responses including MPR and pCR were associated with improved survival, which further reinforce the widely usage of pathological response as surrogate clinical endpoints for long-term survival.[20–22] However, in this study, patients with higher PD-L1 expression did not drive more survival benefit than those with low PD-L1 expression. PD-L1 expression remains the commonly explored biomarker for predicting the response to anti-PD1 therapy in several cancers including lung cancer,[23] melanoma,[24] and gastric cancer,[25] whereas biomarker role of PD-L1 expression was disputable when analyzing the association between PD-L1 expression and the response to a PD-1 blockade.[26] As suggested by ESCORT and ATTRACTION-3 studies, tumor PD-L1 expression was not a robust biomarker of the survival benefit for patients with advanced ESCC.[8,18] The correlation of PD-L1 status and clinical outcomes are warranted for further investigation in ESCC.

There are several limitations to this study. First, this is a retrospective study with inherent selection bias, which needs to be clarified in further prospective research. Second, the sample size of eligible patients in this study is relatively small. Third, follow-up period was relatively short, and further study with longer follow-up period including 3- or 5-year survival rates should be conducted.

Conclusions

A limitation of our study is the absence of a control group. Nevertheless, in our cohort of patients, the neoadjuvant setting, camrelizumab combined with chemotherapy, resulted in good survival outcomes, as well as high rates of MPR and pCR, among patients with locally advanced ESCC. This combination regimens are safe and feasibility, which represents a promising therapeutic option for this population.

Data Sharing Statement

All data generated or analyzed during this study are available upon reasonable request from correspondence author.

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Disclosure

The authors report no conflicts of interest in this work.

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