Analysis of camrelizumab in neoadjuvant chemotherapy for esophageal cancer: A retrospective cohort study

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Abstract. Neoadjuvant therapy has the potential to enhance the prognosis of esophageal squamous cell carcinoma (ESCC). Camrelizumab, a domestically developed programmed cell death protein 1 inhibitor in China, offers a convenient treatment option for Chinese patients with ESCC. The NIC-ESCC2019 trial has demonstrated that the combination of camrelizumab and neoadjuvant chemotherapy has favorable efficacy and tolerable toxicity for resectable ESCC. However, limited real-world comparative data exist regarding its efficacy and safety in Chinese patients with ESCC, necessitating further investigation. The present study aimed to evaluate the clinical efficacy and safety of camrelizumab in combination with paclitaxel and cisplatin for the neoadjuvant treatment of locally advanced ESCC. A retrospective analysis of clinical and pathological data was performed on 70 patients with locally advanced esophageal cancer who underwent neoadjuvant chemotherapy or chemo-immunotherapy followed by radical esophagectomy at Banan Hospital Affiliated to Chongqing Medical University from February 2021 to August 2023. Patients were divided into two groups based on treatment received: A control group (35 patients; neoadjuvant chemotherapy, paclitaxel + cisplatin) and an observation group (35 patients; camrelizumab + paclitaxel + cisplatin). Short-term efficacy, treatment-related adverse reactions (graded using Common Terminology Criteria for Adverse Events v5.0), and postoperative pathological complete remission (pCR) rate were compared. Baseline characteristics were comparable. The observation group had a significantly higher pCR rate compared with the control group (40.0 vs. 8.57%; P=0.002). All patients in the observation group achieved R0 resection, versus 32 (91.4%) in the control group. No grade ≥4 adverse events (AEs) occurred. Reactive cutaneous capillary endothelial proliferation was observed in 45.7% of the observation group (vs. 0% in controls; P<0.05), with no significant differences in other AEs (P>0.05). Neoadjuvant camrelizumab combined with paclitaxel and cisplatin may notably enhance pCR rates in locally advanced ESCC, with a manageable safety profile. The present findings suggest potential clinical benefit, but confirmation through prospective, randomized trials is essential to validate the regimen's efficacy and long-term outcomes.

Introduction

Esophageal cancer (EC) is a highly malignant digestive system cancer with significant incidence and mortality rates. Globally, there were ~604,000 new cases and 544,000 deaths from esophageal cancer annually. It ranks as the seventh most commonly diagnosed cancer and the sixth leading cause of cancer-related deaths worldwide (1). In China, according to the latest data from the National Cancer Center, esophageal cancer is the sixth most common cancer and the fifth leading cause of cancer deaths (2). In China, ESCC accounts for ~90% of esophageal cancer cases, with a particularly high burden in rural and central regions due to risk factors such as smoking, alcohol consumption and diets high in nitrosamines (3). Unfortunately, ESCC is often asymptomatic in early stages, with only 15-20% of patients diagnosed at localized stages. The majority present with advanced disease, characterized by dysphagia, weight loss or obstruction, by which time treatment options are limited and prognosis deteriorates significantly. Despite advances in treatment, its efficacy remains limited, with a 5-year survival rate of approximately 15-20% (4,5). This poor prognosis, coupled with its high prevalence, makes esophageal cancer a major threat to global and Chinese public health. In previous years, immunotherapy, particularly programmed cell death protein 1 (PD-1) inhibitors, has garnered notable attention and application in the treatment of various malignant tumors, with growing evidence supporting its role in neoadjuvant therapy for esophageal cancer. Concurrently, neoadjuvant therapy has emerged as a cornerstone for locally advanced ESCC, primarily aiming to downstage tumors, enhance resectability and mitigate postoperative recurrence (6,7). Camrelizumab, a domestically developed PD-1 inhibitor, offers advantages in accessibility and cost-effectiveness for Chinese patients. Prior studies, such as the NIC-ESCC2019 trial (a multicenter phase 2

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study), demonstrated a 39.2% pathological complete remission (pCR) rate with camrelizumab plus chemotherapy (8,9), but real-world comparative data against chemotherapy alone remain limited.

To address this knowledge gap, a retrospective cohort study was performed to compare outcomes between neoadjuvant hemotherapy alone and camrelizumab-combined therapy in Chinese patients with ESCC. The present study analyzed clinical data from patients who underwent neoadjuvant therapy followed by radical esophagectomy, providing additional insights into the role of camrelizumab in ESCC treatment.

Patients and methods

General information. A total of 70 patients with locally advanced ESCC were retrospectively analyzed and were assigned to groups based on physician discretion and availability of camrelizumab, with 35 receiving neoadjuvant chemotherapy (control group) and 35 receiving camrelizumab plus chemotherapy (observation group) followed by radical esophagectomy. The median age of the control group was 60 years (range 38-78) and comprised 22 men and 13 women. The media age of the observation group was 62 years (range 34-76), comprising 21 men and 14 women. The inclusion criteria was as follows: i) Histopathologically confirmed esophageal squamous cell carcinoma; ii) presence of measurable lesions [as per response evaluation criteria in solid tumors (RECIST) 1.1 criteria]; iii) receipt of preoperative neoadjuvant chemotherapy (paclitaxel + cisplatin) with or without camrelizumab; and iv) Karnofsky performance status (KPS) ≥70 points. The exclusion criteria included: i) Age >80 years; ii) severe cardiovascular and cerebrovascular disorders; iii) distant metastasis or severe autoimmune ailments; and iv) cervical esophageal cancer. The present research has been registered in the Chinese Medical Research Registration Information System (registration no. MR-50-24-002195). The protocol of the present study was approved by the Ethics Committee of the Banan Hospital Affiliated to Chongqing Medical University (approval no. R2024009) and written informed consent was obtained from all participants.

Treatment methods. The control group received 2-4 cycles of paclitaxel (150 mg/m^2) and cisplatin (50 mg/m^2) every 2 weeks. The observation group received 4 cycles of camrelizumab (200 mg) every 3 weeks in addition to chemotherapy. The surgical technique employed was McKeown esophagectomy with two-field lymphadenectomy, and esophageal reconstruction was achieved using a stomach conduit and cervical anastomosis.

Observation indexes

Imaging efficacy evaluation. Response was assessed using contrast-enhanced CT scans by two independent reviewers using RECIST v1.1 criteria. The criteria for the responses were as follows: i) CR where the cancer disappeared completely after treatment for >4 weeks; ii) partial remission (PR), where although the cancer did not completely disappear after treatment, the sum of the longest diameter and the perpendicular diameter decreased by >50% compared with before treatment; iii) stable disease (SD) where the sum of the longest diameter of the cancer did not reach the criteria for PR but showed a decrease over >4 weeks, or the increase did not reach the criteria for disease progression, or the sum of the products of the longest diameter and the perpendicular diameter of each lesion decreased by <50% compared with before treatment or the increase was ≤25%; and iv) progressive disease (PD) where the sum of the longest diameters of the cancer increased by >25% compared with before treatment, new cancer lesions appeared or new cancerous pleural effusion and ascites appeared. The objective response rate (ORR) and disease control rate (DCR) were calculated as follows: ORR=CR rate + PR rate; DCR=CR rate + PR rate + SD rate.

Pathological efficacy evaluation. Tumor regression grade (TRG) was retrospectively evaluated by pathologists according to the 7th edition of the American Joint Committee on Cancer (AJCC) grading system, using the pathological specimens of postoperative patients. The evaluation criteria were as follows: TRG0 (pCR and no residual cancer cells) and TRG1-3 (varying degrees of tumor regression). pCR describes the absence of invasive cancer in the primary lesion and no detectable cancer cells in the lymph nodes. Major pathological response indicates ≤10% residual tumor cells in the resected esophageal and lymph node tissues.

Effect of malignant tumor resection. The efficacy of malignant tumor resection is typically assessed based on the extent of resection and the status of the resection margin, which can be categorized into three types: R0, R1 and R2 resections. The evaluation criteria used were as follows: R0 resection was the complete removal of the tumor, with negative microscopic margins indicating the absence of any tumor residue; R1 resection was achieved when the tumor was visibly removed in its entirety, but tumor cells were detected at the resection margin upon microscopic examination; and R2 resection was incomplete resection, where the remaining tumor was visible to the naked eye.

Adverse events (AEs) during neoadjuvant therapy. The toxicity of neoadjuvant therapy was monitored according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 5.0. AEs such as anemia, bone marrow suppression, liver dysfunction, renal dysfunction, cardiovascular adverse reactions, reactive skin capillary hyperplasia, hair loss, gastrointestinal symptoms, limb numbness and other conditions experienced during drug treatment were analyzed in both groups.

Statistical analysis. Continuous variables conforming to a normal distribution were presented as the mean ± standard deviation (SD), while non-normally distributed continuous variables were presented as the median and interquartile range (IQR). Data normality was tested using the Shapiro-Wilk test; parametric tests were applied for normal distributions. Categorical variables were described as frequencies and percentages. Independent-sample t-tests or Mann-Whitney U tests were used to compare continuous variables. For categorical variables, a χ^2 test was used when the expected count in <20% of cells was ≥5; otherwise, a Fisher's exact test was applied. In the present study, two-sided P-values <0.05 were considered to indicate a statistically significant difference.

Table I. Comparison of preoperative clinical characteristics between the two groups.

General data	Control group (n=35)	Observation group (n=35)	t/χ^2	P-value
Age, years	59.83±8.32	61.49±9.58	0.773	0.442
Sex			0.060	0.806
Male	22 (62.9)	21 (60.0)		
Female	13 (37.1)	14 (40.0)		
Tumor location			0.701	0.704
Proximal third	10 (28.6)	7 (20.0)		
Middle third	18 (51.4)	20 (57.1)		
Distal third	7 (20.0)	8 (22.9)		
Clinical T stage				0.797
cT1	0 (0.0)	0 (0.0)		
cT2	0 (0.0)	1 (2.9)		
cT3	10 (28.6)	11 (31.4)		
cT4	25 (71.4)	23 (65.7)		
Clinical N stage				0.864
cN0	22 (62.9)	24 (68.6)		
cN1	10 (28.6)	9 (25.7)		
cN2	3 (8.6)	2 (5.7)		
cN3	0 (0.0)	0 (0.0)		
Clinical TNM stage				0.467
II	2 (5.7)	4 (11.4)		
III	20 (57.1)	22 (62.9)		
IV	13 (37.1)	9 (25.7)		

Data presented as n (%). T, tumor stage; N, lymph node stage; M, metastasis stage.

Statistical analysis was performed using SPSS 23.0 for Windows (IBM Corp).

Results

Comparison of patient characteristics. A total of 70 patients were enrolled in the present study. No missing data were encountered in primary outcome measures; therefore, no incomplete baseline data were excluded (n=0). The control group comprised 35 patients, with an average age of 59.83±8.32 years, including 22 men and 13 women. Tumor locations were distributed as follows: A total of 10 cases in the proximal third, 18 cases in the middle third and 7 cases in the distal third. The observation group consisted of 35 patients, with an average age of 61.49±9.58 years, including 21 men and 14 women. Tumor locations were reported as 7 cases in the proximal third, 20 cases in the middle third and 8 cases in the distal third. Clinical tumor, lymph node, metastasis (TNM) stages were as follows: Stage II (5.7%), III (57.1%), IV (37.1%) in the control group; and stage II (11.4%), III (62.9%), IV (25.7%) in the observation group. No significant differences were observed in age, sex, tumor location and TNM stage between the two groups (P>0.05), indicating comparability. Detailed information is presented in Table I.

Comparison of short-term efficacy. ORR was 80.0% (28/35) in the observation group vs. 45.7% (16/35) in the control group (P=0.003). Detailed data are presented in Table II. In the observation group, the pCR rate was significantly higher compared with the control group (40.0 vs. 8.6%; P=0.002). All patients in the observation group achieved complete resection (R0), whereas 32 patients (91.4%) achieved R0 resection in the control group. Further information is provided in Table III.

Comparison of incidence of AEs. All AEs were graded per CTCAE v5.0. No grade ≥4 AEs were observed in either group. In the observation group, the incidence of reactive cutaneous capillary endothelial proliferation (RCCEP) was 45.7% (16/35), while no cases were observed in the control group. These results showed a statistically significant difference between the groups (P<0.05). Immune-related AEs (irAEs) were systematically monitored throughout the study. Camrelizumab-associated RCCEP, which is predominantly mild, reversible and confined to the skin surface, was managed with standard local skincare. All RCCEP cases resolved within 1-2 months following treatment discontinuation, and none required extended interventions or alternative management strategies. However, no significant differences were observed in the rates of anemia, bone marrow suppression, elevated liver enzymes, abnormal renal function, cardiovascular adverse reactions, hair loss, gastrointestinal symptoms or limb numbness between the observation group and the control group (P>0.05), as shown in Table IV.

Table II. Comparison of imaging efficacy between the two groups.

Efficacy	Control group (n=35)	Observation group (n=35)	χ^2	P-value
Complete remission	2 (5.7)	8 (22.9)		
Partial remission	14 (40.0)	20 (57.1)		
Stable disease	16 (45.7)	7 (20.0)		
Progressive disease	3 (8.6)	0 (0.0)		
Objective response rate	16 (45.7)	28 (80.0)	8.811	0.003
Disease control rate	32 (91.4)	35 (100.0)	3.134	0.077

Data presented as n (%).

Table III. Postoperative pathological evaluation of the two groups of patients.

Efficacy	Control group (n=35)	Observation group (n=35)	χ^2	P-value
Tumor regression grade				
0	3 (8.6)	14 (40.0)	9.401	0.002
1	8 (22.9)	10 (28.6)	0.299	0.584
2	15 (42.9)	8 (22.9)	3.173	0.075
3	9 (25.7)	3 (8.6)	3.621	0.057
Pathological complete remission	3 (8.6)	14 (40.0)	9.401	0.002
Major pathological response	11 (31.4)	24 (68.6)	9.657	0.002
R0	35 (100.0)	32 (91.4)		0.239

Data presented as n (%). R0, complete resection.

Table IV. Comparison of the incidence of adverse reactions between the two groups.

	Control group (n=35)		Observation group (n=35)			
Adverse reactions	Any	Grade ≥3	Any	Grade ≥3	χ^2	P-value
Anemia	8 (22.9)	1 (2.9)	6 (17.1)	0 (0.0)	0.357	0.550
Myelosuppression	11 (31.4)	0 (0.0)	14 (40.0)	1 (2.9)	0.560	0.454
Elevated liver enzymes	5 (14.3)	0 (0.0)	4 (11.4)	0 (0.0)		>0.999
Renal dysfunction	1 (2.9)	0 (0.0)	2 (5.7)	0 (0.0)		>0.999
Cardiovascular adverse reactions	3 (8.6)	0 (0.0)	2 (5.7)	0 (0.0)		>0.999
Reactive cutaneous capillary endothelial proliferation	0 (0.0)	0 (0.0)	16 (45.7)	0 (0.0)	20.741	<0.001
Alopecia	17 (48.6)	0 (0.0)	21 (60.0)	0 (0.0)	0.921	0.337
Gastrointestinal symptoms	13 (37.1)	0 (0.0)	15 (42.9)	0 (0.0)	0.238	0.626
Numbness of limbs	9 (25.7)	0 (0.0)	7 (20.0)	0 (0.0)	0.400	0.527

Data presented as n (%). Statistical analyses are based on data from the 'Any' columns of both groups, excluding grade ≥3 data.

Discussion

According to statistical data from the National Cancer Center, the incidence and mortality rates of esophageal cancer in China in 2020 were 13.8/100,000 and 12.7/100,000, ranking sixth and fourth among malignant tumors, respectively (10). ESCC accounts for ~90% of esophageal cancer cases in China (11). In previous years, the approach to treating esophageal cancer has evolved from simple surgical interventions to comprehensive surgical-based treatments, with neoadjuvant therapy emerging as a cornerstone in managing locally advanced resectable esophageal cancer. Neoadjuvant therapy refers to the administration of relevant treatment before surgery, aiming to reduce the tumor size and extent or downgrade the tumor stage,

thereby enhancing surgical outcomes and reducing the risk of tumor recurrence and metastasis (12,13).

Since its initial report in the New England Journal of Medicine in 2012 (14), neoadjuvant concurrent chemoradiotherapy has been adopted as the global standard for managing locally advanced resectable esophageal/esophagogastric junction cancer. Moreover, research advancements from Yang *et al* (15) have revealed that neoadjuvant chemoradiotherapy confers substantial survival benefits in locally advanced resectable ESCC, offering more precise guidance for treating this condition in China (15). Despite the high incidence and poor prognosis of esophageal cancer, comprehensive treatment strategies such as neoadjuvant therapy result in improved patient outcomes and enhanced quality of life.

In previous years, immunotherapy has been widely adopted in tumor treatment, with PD-1 inhibitors marking a major breakthrough and emerging as a novel research avenue in esophageal cancer treatment (16,17). Camrelizumab, an independently developed PD-1 inhibitor in China, functions by obstructing the binding of PD-1 and programmed death-ligand 1 (PD-L1), thereby disrupting the PD-1/PD-L1 signaling pathway and inhibiting tumor cell proliferation. Its efficacy has been demonstrated across various malignant tumors, including Hodgkin's lymphoma, hepatocellular carcinoma, non-small cell lung cancer, ESCC and nasopharyngeal carcinoma (18-24). Research indicates that preoperative camrelizumab can enhance the R0 resection rate in patients with locally advanced esophageal cancer, and when combined with chemotherapy, can markedly prolong patient median survival time (25). In a multicenter trial investigating locally advanced resectable ESCC, the combination of two cycles of neoadjuvant chemotherapy with camrelizumab yielded a notable pCR rate of 39.2%, with a surgical R0 resection rate reaching 98% (26). Previous studies (27-29) have also reported satisfactory outcomes with neoadjuvant chemotherapy combined with camrelizumab in the treatment of locally advanced resectable ESCC, with a pCR rate >30% and an R0 resection rate >90%.

The enhanced pCR rates observed with camrelizumab in ESCC arise from synergistic immunomodulatory mechanisms (30). As a selective PD-1 inhibitor, camrelizumab disrupts PD-1/PD-L1 signaling through sustained receptor internalization, reversing T-cell exhaustion and amplifying cytotoxic $CD8^+$ T-cell infiltration into tumor cores (31). This checkpoint blockade synergizes with chemotherapy-induced immunogenic priming: Paclitaxel/cisplatin promote tumor antigen release, upregulate PD-L1 expression via IFN-γ/STAT1 signaling and trigger immunogenic cell death to enhance dendritic cell activation (32). Concurrently, the regimen remodels the tumor microenvironment by suppressing immunosuppressive cancer-associated fibroblasts, normalizing aberrant vasculature and alleviating metabolic acidosis to restore T-cell functionality (33). The temporal coordination between chemotherapy-induced immunogenic 'priming' and camrelizumab-driven immune 'amplification' establishes a self-reinforcing antitumor cycle (34), collectively driving superior pCR outcomes.

In the present study, the observation group exhibited a significantly higher pCR rate compared with the control group (40.0 vs. 8.6%). Additionally, all patients in the observation group achieved complete resection (R0), whereas only 32 patients (91.4%) in the control group achieved R0 resection. No grade ≥4 AEs were observed in either group. AEs induced by chemotherapy drugs in both groups were mild and manageable and did not impede the treatment regimen. In the observation group, the incidence of RCCEP was 45.7% (16 out of 35), whereas no cases were observed in the control group. All RCCEP cases resolved within 1-2 months following treatment discontinuation, and none required extended interventions or alternative management strategies. Symptomatic management, including local skin care and appropriate anti-inflammatory measures, was administered to a few patients. Camrelizumab-related RCCEP is predominantly mild, reversible and occurs exclusively on the skin surface. This observation aligns with prior reports on RCCEP in camrelizumab-treated populations (35). This reaction may be attributed to the potential of camrelizumab to promote capillary proliferation in conjunction with vascular endothelial growth factor (36). Camrelizumab monotherapy may lead to such AEs, but its incidence can be markedly reduced by concurrent treatment with targeted anti-angiogenic drugs (37).

In summary, the combination of camrelizumab, paclitaxel and cisplatin as a neoadjuvant therapy for locally advanced esophageal cancer shows notable clinical efficacy and manageable safety. Compared with neoadjuvant chemotherapy alone, the combination therapy offered benefits in antitumor activity without increased AEs. However, several limitations must be acknowledged. First, the retrospective design introduces potential selection biases, particularly in patient inclusion criteria and treatment allocation, which may influence the representativeness of the cohort. Second, the relatively small sample size (n=70) reduces statistical power to detect subtle differences in outcomes and limits the generalizability of findings to broader populations. Furthermore, the limited follow-up duration in the present study precludes robust analysis of long-term survival outcomes (such as 5-year overall survival) and late-onset treatment-related toxicities. To address this, the follow-up is being actively expanded for this cohort through to 2028, with planned analyses of 5-year overall survival and recurrence-free survival. To address these limitations, future multicenter prospective studies with larger cohorts and extended follow-up periods are warranted to validate the findings.

In conclusion, neoadjuvant camrelizumab combined with paclitaxel and cisplatin may notably enhance pCR rates in locally advanced ESCC, with a manageable safety profile. These findings suggest potential clinical benefit, but confirmation through prospective, randomized trials is essential to validate the regimen's efficacy and long-term outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JL and JZ contributed to study conception, design, data collection and organization, analysis and interpretation. JL led manuscript drafting and JZ reviewed it. BC provided insights and expertise, assisted in data analysis and interpretation, and offered manuscript improvement suggestions. JL and JZ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The protocol of the present study was approved by the Ethics Committee of the Banan Hospital Affiliated to Chongqing Medical University (approval no. R2024009) and written informed consent was obtained from all participants.

Patient consent for publication

The patients provided written informed consent for publication of the data in the present manuscript.

Competing interests

The authors declare that they have no competing interests.

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