Original Article

Real-world retrospective study of anti-PD-1 antibody in combination with chemotherapy as a neoadjuvant treatment strategy for locally advanced resectable esophageal squamous cell carcinoma

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Background: Neoadjuvant therapy has become a mainstay of treatment for locally advanced resectable esophageal cancer. The objective of this research was to investigate the effectiveness and safety of neoadjuvant immunotherapy combined with chemotherapy in treating surgically removable esophageal squamous cell carcinoma (ESCC).

Methods: From January 1, 2016 to April 1, 2023, we conducted a retrospective analysis of patients diagnosed with resectable esophageal cancer who underwent neoadjuvant immunotherapy combined with chemotherapy at The First Affiliated Hospital of Nanchang University. The primary endpoints of this study were pathologic complete response (pCR), major pathologic response (MPR) and disease-free survival (DFS). The secondary endpoints of this study were overall survival (OS), objective response rate (ORR) and safety.

Results: A total of 122 patients with ESCC receiving neoadjuvant immune-chemotherapy (nICT) were included. Fifty-four patients achieved partial response (PR) and two patients achieved complete response (CR), with an ORR of 45.9%. Of the 106 patients who underwent surgery, a total of 28 patients achieved pCR (26.4%) and a total of 37 patients achieved MPR (34.9%). Grade 3 or higher adverse events occurred in 26 patients (21.3%). The most common postoperative complication was pneumonitis (25.5%).

Conclusions: Neoadjuvant immunotherapy combined with chemotherapy demonstrates satisfactory efficacy in the treatment of locally advanced ESCC, with manageable treatment-related adverse events and postoperative complications.

Keywords: Resectable esophageal carcinoma; neoadjuvant therapy; immunotherapy; anti-programmed death-1 antibody (anti-PD-1 antibody); chemotherapy

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Introduction

Esophageal cancer is the eighth most common cancer in the world, and the sixth in mortality (1). Esophageal adenocarcinoma is mostly found in Western countries, while more than 90% of esophageal squamous cell carcinomas (ESCCs) are present in China (2). Although esophagectomy is considered the primary treatment option for early-stage esophageal cancer, the majority of patients are diagnosed with locally advanced disease, resulting in a low rate of successful complete resection (R0) and an increased risk of postoperative recurrence and metastasis (3). According to the CROSS study and the NEOCRTEC5010 studies, the addition of preoperative chemoradiotherapy has been found to enhance the overall survival (OS) of patients with esophageal cancer compared to surgery alone. As a result, this treatment approach has been incorporated into the recommendations of both the National Comprehensive Cancer Network (NCCN) and the Chinese Society of Clinical Oncology (CSCO) guidelines (4,5). However, according to follow-up data after 10 years in the CROSS study, approximately 40% of patients who received preoperative chemoradiotherapy plus surgery developed distant metastases (6). Hence, it is imperative to investigate a neoadjuvant treatment regimen that offers enhanced efficacy and greater safety for patients with esophageal cancer.

Due to extensive research and successful utilization of immunotherapy in malignancies like melanoma, non-small cell lung cancer, and kidney cancer (7), immunotherapy has emerged as a recommended therapeutic option for managing advanced or metastatic esophageal cancer. Investigations into neoadjuvant immunotherapy for esophageal cancer are progressively unraveling, and there is an anticipated advancement in the efficacy and safety of treatment through the exploration of neoadjuvant immunotherapy in combination with chemotherapy for esophageal cancer. Preclinical studies have shown that most chemotherapy drugs can cause immunostimulatory effects by inhibiting immunosuppressive cells, activating effector cells, and increasing the infiltration of T cells in tumor tissues, and the integration of immunotherapy with chemotherapy can potentiate the immune response, leading to even greater enhancement of treatment efficacy (8). In a study conducted by Shen *et al*., the safety and efficacy of neoadjuvant immunotherapy combined with chemotherapy were evaluated in patients with locally advanced resectable ESCC. Compared to simple chemotherapy, it demonstrated unprecedented rates of R0 resection and pathologic complete response (pCR). The researchers also found that the combination of immunotherapy and chemotherapy made the tumor adhere more loosely to the surrounding tissue, making it less difficult to remove surgically (9). Cheng *et al*. conducted a comparative analysis of the effectiveness and safety between neoadjuvant immunochemotherapy and neoadjuvant chemoradiotherapy (nCRT) (10). The findings revealed comparable rates of pCR and the occurrence of grade III and higher adverse events in both treatment groups. Nevertheless, the nCRT group exhibited a notably higher frequency of postoperative complications compared to the neoadjuvant immune-chemotherapy (nICT) group. This elevated incidence can be attributed to thoracic tissue injury and pleural adhesion induced by radiotherapy, leading to a significant rise in the occurrence of postoperative complications such as anastomotic leakage and pleural effusion. These factors collectively contribute to heightened surgical challenges. The findings imply that the combination of neoadjuvant immunotherapy and chemotherapy is more effective than neoadjuvant chemotherapy alone. Additionally, this combined approach is associated with a decreased likelihood of postoperative complications and an enhanced level of postoperative safety when compared to nCRT.

Highlight box

Key findings

- The combination of neoadjuvant immunotherapy with chemotherapy for the treatment of locally advanced esophageal squamous cell carcinoma (ESCC) has shown satisfactory therapeutic efficacy, with manageable treatment-related adverse events and postoperative complications.

What is known and what is new?

- Neoadjuvant chemoradiotherapy is the standard approach for the neoadjuvant treatment of locally advanced esophageal malignancies, but it is associated with a high incidence of adverse events and poor patient compliance. Immunotherapy has been recommended for the treatment of advanced or metastatic esophageal cancer.
- This study explored the therapeutic efficacy and safety of neoadjuvant immunotherapy combined with chemotherapy in resectable ESCC.

What is the implication, and what should change now?

- The combination of neoadjuvant immunotherapy with chemotherapy can serve as a novel treatment approach for locally advanced resectable esophageal cancer, requiring further assessment of safety and effectiveness.

Evidence suggests a correlation between tumor cells and inflammatory cells (11). The neutrophil-to-lymphocyte ratio (NLR) is considered a marker of systemic inflammation (12). In a retrospective study carried out by Hoshino *et al*., it was observed that NLR during relapse could serve as a prognostic biomarker for ESCC (13). Elevated NLR was found to be correlated with increased recurrence of ESCC tumors and a poorer prognosis. Viñal *et al.* investigated the relationship between NLR and the prognosis of cancer patients undergoing immunotherapy, and the findings revealed that both the initial NLR and the trend in NLR over time independently influenced the survival outcomes of cancer patients receiving immunotherapy (14). Proteins associated with tumors have the capability to be generated and released into the bloodstream. Detecting these proteins can aid in identifying tumors, as well as predicting the prognosis and response to treatment. Tumor markers such as cytokeratin 19 fragment antigen 21-1 (CYFRA 21-1) have been reported as predictive markers for ESCC progression (15). Nonetheless, the optimal tumor marker for predicting the prognosis of individuals with ESCC is still under investigation.

In view of the fact that neoadjuvant immunotherapy combined with chemotherapy for esophageal cancer is currently in the exploratory stage, the primary objective of this study was to investigate the effectiveness and safety of neoadjuvant immunotherapy in individuals with resectable ESCC. We also preliminarily investigated the prognostic association of NLR and tumor markers with neoadjuvant immunotherapy for esophageal cancer. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-169/rc).

Methods

Inclusion and exclusion criteria

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Affiliated Hospital, Nanchang University (No. IIT-2023335). Individual consent for this retrospective analysis was waived. This is a retrospective, single-center, observational study. A retrospective analysis was performed for patients with resectable esophageal cancer in The First Affiliated Hospital of Nanchang University from January 1, 2016 to April 1, 2023. The inclusion criteria for patients were as follows: (I) diagnosed histopathologically as ESCC; (II) age greater than or equal to 18 years; (III) Eastern Cooperative Oncology Group (ECOG) performance status score 0–1; (IV) the clinical stage of II–IVA ESCC (T2–4aNxM0); (V) assessed by a multidisciplinary clinical team for surgical resection; (VI) with adequate organ and bone marrow function; (VII) administered with neoadjuvant immunotherapy combined with chemotherapy. The exclusion criteria for patients were as follows: (I) patients with other pathological subtypes of esophageal malignancies, such as adenocarcinoma, neuroendocrine carcinoma, large cell undifferentiated carcinoma, etc.; (II) diagnosis of other malignant tumors within the past 5 years; (III) patients who had received prior radiotherapy, targeted therapy, chemotherapy or other immunosuppressant therapy; (IV) patients who cannot undergo surgery due to poor cardiac or lung function; (V) active autoimmune disease or infectious disease; (VI) patients on ongoing systemic corticosteroid therapy.

Treatment options

Neoadjuvant immunotherapy included six PD-(L) 1 inhibitors, pembrolizumab (200 mg, q3w), tislelizumab (200 mg, q3w), camrelizumab (200 mg, q3w), sintilimab (200 mg, q3w), nivolumab (240 mg, q3w), and toripalimab (240 mg, q3w). The chemotherapy regimen consisted of paclitaxel plus platinum-based agents, specifically: paclitaxel (135–175 mg/m^2, q3w) + cisplatin (75–100 mg/m^2, q3w)/nedaplatin (80–100 mg/m^2, q3w)/carboplatin [area under the curve (AUC) =5, q3w]. Esophagectomy was usually performed within 4–6 weeks of completing the nICT. Esophagectomy includes right thorax-epigastric two-incision esophagectomy (Ivor-Lewis method) and left cervical-right thorax-epigastric midline three-incision esophagectomy (McKeown method). Lymph node dissection includes two-field lymph node dissection (thoracoabdominal + superior mediastinum) and three-field lymph node dissection (bilateral lower neck and supraclavicular + thoracoabdominal + superior mediastinum).

Efficacy evaluation and safety monitoring

The efficacy was evaluated according to the comparison of the patient's imaging data before the first neoadjuvant therapy and the last time before surgery. After two–four cycles of neoadjuvant therapy, the patient underwent a preoperative evaluation. The evaluation criteria refer to the

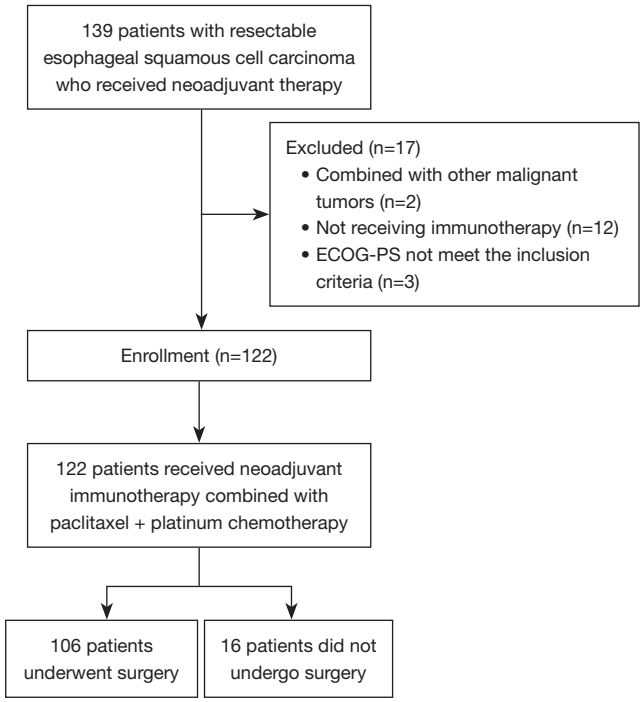


Figure 1 Patient selection flowchart. ECOG-PS, Eastern Cooperative Oncology Group performance status.

Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (16). It was divided into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). After surgery, the efficacy was evaluated according to the pathological tumor regression grade (TRG) after esophagectomy. TRG was assessed by the proportion of scar to residual tumor, graded by the Ryan's TRG system: grade 0 for no residual tumor, grade 1 for residual single tumor cells or small groups of tumor cells, grade 2 for residual partial tumor, and grade 3 for no regression (17). The major pathologic response (MPR) was defined as less than 10% residual tumor cells, and pCR was defined as the absence of evidence of residual tumor cells (18). The safety of treatment was primarily assessed by the frequency and severity of treatment-related adverse effects. Safety was assessed by monitoring hematological parameters, clinical symptoms, and vital signs. Adverse events and complications that occurred during treatment are closely observed and recorded. The grading criteria for adverse reactions were based on the Common Adverse Reaction Terminology Criteria version 5.0 (CTCAE5.0). Postoperative complications within 30 days of surgery took reference of the Clavien-Dindo classification (19).

Statistical analysis

The primary endpoints of this study were pCR, MPR and disease-free survival (DFS). The secondary endpoints of this study were OS, objective response rate (ORR) and safety. ORR was defined as the proportion of patients whose tumor had shrunk to a predetermined value and maintained the minimum time limit, which was the sum of the proportion of CR and PR. DFS was defined as the time (in months) from the onset of randomization to disease recurrence or death or the last follow-up. OS was defined as the time (in months) from the onset of randomization to death or last follow-up.

SPSS26.0 was used for statistical analysis. Data such as baseline demographic characteristics, safety data, and pathological response were analyzed using descriptive statistical analysis, where continuous variables were described as medians and ranges, and categorical variables were described as frequencies and percentages. Continuous data from patients in the MPR and non-MPR groups were compared using the non-parametric Mann-Whitney *U*-test. The relationship between continuous variables and immunotherapy MPR was assessed using Chi-square test. The Kaplan-Meier method and Cox proportional hazards model [including hazard ratio (HR) and 95% confidence interval (CI)] were used to assess DFS and OS, and the log-rank test was used for statistical significance analysis. $P<0.05$ was statistically significant.

Results

Baseline demographic and clinical characteristics

A total of 122 patients with ESCC were enrolled from January 1, 2016 to April 1, 2023 (*Figure 1*). The median age was 65 years (range, 41–78 years). Of these, 104 were male (85.2%) and 18 were female (14.8%). Due to the higher number of male patients, both smoking history (81/122, 66.4%) and alcohol history (70/122, 57.4%) were higher. Stage II (22/122, 18.0%) was diagnosed with 22 patients, stage III (90/122, 73.8%) was diagnosed with 90 patients, and only 10 patients were diagnosed with stage IV (10/122, 8.2%). The majority of all patients received two cycles of neoadjuvant therapy (89/106, 84.0%). Seventeen patients (17/106, 16.0%) who underwent more than two cycles of neoadjuvant therapy. These patients received more than two cycles of neoadjuvant therapy for the following reasons. Nine patients (9/17, 52.9%) did not show significant reduction in lymph nodes based

on preoperative imaging assessment. Six patients (6/17, 35.3%) did not show significant reduction in tumor size based on preoperative imaging assessment. Two patients (2/17, 11.8%) received more than two cycles of neoadjuvant therapy due to personal reasons. Eleven patients (11/122, 9.0%) received postoperative radiotherapy, with six (6/11, 54.5%) undergoing lymph node radiotherapy due to lymph node recurrence metastasis, three (3/11, 27.3%) receiving brain radiotherapy due to brain metastasis, and two (2/11, 18.2%) receiving bone radiotherapy due to bone metastasis. Baseline demographics and clinical features are summarized in *Table 1*.

Efficacy

Of the 122 patients included in this study, 106 underwent surgery and 16 did not, of whom 6 did not undergo surgery due to disease progression, 10 had indications for surgery and refused surgery for personal reasons, and those who did not undergo surgery received chemotherapy, radiotherapy, or immunotherapy. Postoperative pathology showed that 59 patients were stage IA–IIB (55.7%) and 47 cases were stage IIIA–IVA (44.3%). Postoperative pathological reactions showed that a total of 28 patients achieved pCR (26.4%) and a total of 37 patients achieved MPR (34.9%). Postoperative pathological tumor regression was graded and showed TRG 0 (26.4%) in 28 patients, TRG 1 (18.9%) in 20 patients, TRG 2 (28.3%) in 30 patients, and TRG 3 (26.4%) in 28 patients. According to RECIST 1.1, the efficacy of neoadjuvant therapy was assessed as PR (44.3%) in 54 patients, CR (1.6%) in 2 patients, SD (49.2%) in 60 patients, and an ORR of 45.9%, and a disease control rate (DCR) of 95.1%.

Correlation between neoadjuvant therapy cycle, NLR changes and therapeutic efficacy

According to the postoperative pathological remission, the patients were divided into MPR group and non-MPR group. Therapeutic efficacy comparison had been made between patients who received two courses and those who received three or more courses, but there was no difference in the results (P=0.81) (Table S1). The NLR before neoadjuvant therapy and as well as before surgery were compared between the two groups. The results showed that there was no difference in NLR before neoadjuvant therapy between the MPR group and the non-MPR group (P=0.66) (Table S1). However, patients in the MPR group had a lower last NLR before surgery compared with the non-MPR group (median 1.74 *vs.* 2.47, P=0.003) (Table S1). ΔNLR was defined as the ratio of the last NLR before surgery to the NLR before neoadjuvant therapy. When ΔNLR <1, it indicates a decrease in NLR, and when ΔNLR ≥1, it indicates an increase or no change in NLR. Next, we analyzed the changes in NLR, and the results showed that a decrease in NLR was associated with a higher probability of achieving MPR compared to an increase in NLR (74.3% *vs.* 31.3%, P=0.001) (Table S1). *Figure 2* illustrates the distribution of ΔNLR in the MPR and non-MPR groups, revealing that patients with an increase in NLR were more concentrated in the non-MPR group.

Survival analysis and prognostic factors

As of 1 April, 2023, the median follow-up was 14.1 months (range, 3.0 to 31.3 months). In the entire cohort, the 1-year OS rate and the 2-year OS rate were 90.8% and 81.0%, respectively (*Figure 3A*). The DFS rates at 1-year and 2-year in surgical patients were 94.4% and 86.0%, respectively (*Figure 3B*). The 2-year DFS rate of patients who achieved CR or PR in preoperative imaging efficacy evaluation was significantly higher than that in patients who achieved SD or PD (83.2% *vs.* 59.8%, P=0.04) (*Figure 4A*). The 2-year DFS rate of patients with postoperative stage I–II was significantly higher than that of patients with postoperative stage III–IV (96.4% *vs.* 55.0%, P=0.001) (*Figure 4B*). The 2-year DFS rate of patients with negative lymph nodes in postoperative pathology was significantly higher than that of patients with positive lymph nodes (96.1% *vs.* 62.6%, P=0.02) (*Figure 4C*). According to the receiver operating characteristic (ROC) curve, the optimal cut-off value of preoperative NLR was obtained. According to the optimal cut-off value, the NLR was divided into high NLR group and low NLR group, and the results showed that the 2-year DFS rate in the low NLR group was significantly higher than that in the high NLR group (85.2% *vs.* 50.8%, P=0.04) (*Figure 4D*).

The 2-year OS rate of patients who achieved CR or PR in preoperative imaging efficacy evaluation was significantly higher than that in patients who achieved SD or PD (89% *vs.* 63.8%, P=0.02) (*Figure 5A*). The 2-year OS rate of patients with postoperative stage I–II was significantly higher than that of patients with postoperative stage III–IV (96.3% *vs.* 66.4%, P=0.001) (*Figure 5B*). The 2-year OS rate of patients with negative lymph nodes after surgery was significantly higher than that of patients with positive lymph

Table 1 Baseline demographic and clinical characteristics

Features	All patients (N=122)
Age (years), median [range]	65 [41–78]
Sex, n (%)	
Male	104 (85.2)
Female	18 (14.8)
Smoking history, n (%)	81 (66.4)
Drinking history, n (%)	70 (57.4)
Tumor location, n (%)	
Upper	7 (5.7)
Middle	40 (32.8)
Lower	67 (54.9)
Unable to assess	8 (6.6)
Clinical T stage, n (%)	
cT2	12 (9.8)
cT3	102 (83.6)
cT4	8 (6.6)
Clinical N stage, n (%)	
cN0	17 (13.9)
cN1	45 (36.9)
cN2	55 (45.1)
cN3	5 (4.1)
Clinical stage, n (%)	
II	22 (18.0)
III	90 (73.8)
IV	10 (8.2)
Pathological classification, n (%)	
Ulcerative type	21 (17.2)
Infiltrative type	6 (4.9)
Constrictive type	6 (4.9)
Medullary type	13 (10.7)
Protruding type	6 (4.9)
Fungating type	1 (0.8)
Unable to assess	69 (56.6)
Differentiation degree, n (%)	
Poorly differentiated	20 (16.4)
Moderately differentiated	64 (52.5)
Well-differentiated	11 (9.0)
Unable to assess	27 (22.1)
Depth of invasion, n (%)	
Carcinoma *in situ*	27 (22.1)
Mucosa layer	10 (8.2)
Submucosa	14 (11.5)
Muscularis propria	23 (18.9)
Adventitia	32 (26.2)
Unable to assess (no surgery was performed)	16 (13.1)
Surgical treatment, n (%)	106 (86.9)
Surgical procedure, n (%)	
McKeown method	81 (76.4)
Ivor-Lewis method	25 (23.6)
Lymph node dissection, n (%)	
Three-field lymph node dissection	28 (26.4)
Two-field lymph node dissection	78 (73.6)
Neoadjuvant therapy cycle (nICT), n (%)	
2	89 (84.0)
>2	17 (16.0)
Postoperative radiation therapy, n (%)	11 (9.0)
PD-1 inhibitors, n (%)	
Camrelizumab	46 (37.7)
Nivolumab	29 (23.8)
Tislelizumab	20 (16.4)
Pembrolizumab	11 (9.0)
Toripalimab	9 (7.4)
Sintilimab	7 (5.7)
Chemotherapy regimen, n (%)	
Paclitaxel plus nedaplatin	101 (82.8)
Paclitaxel plus cisplatin	18 (14.8)
Paclitaxel plus carboplatin	3 (2.5)
Interval to surgery (days), mean (IQR)	41.8 (35.8–44.3)

T, tumor; N, node; nICT, neoadjuvant immune-chemotherapy; PD-1, programmed death-1; IQR, interquartile range.

nodes (95.9% *vs.* 65.4%, P=0.02) (*Figure 5C*). The 2-year OS rate in the low NLR group was significantly higher than that in the high NLR group (85.7% *vs.* 52.0%, P=0.03) (*Figure 5D*).

Further analysis for tumor biomarkers indicated that patients with low carbohydrate antigen 125 (CA125), low CYFRA21-1, low alpha fetoprotein (AFP), and low squamous cell carcinoma antigen (SCCA) seem to obtained better DFS and OS (*Figures 6*,*7*).

To better analyze the prognostic factors of patients, univariate analyses were performed and the outcomes are summarized in *Table 2*. On univariable analysis for prognosis, ypI–II, ypN–, low-NLR, low-CA125, low-SCCA had better DFS (P=0.004; P=0.04; P=0.046; P=0.043; P=0.04) and OS (P=0.004; P=0.041; P=0.04; P=0.04; P=0.047). Multivariate analyses did not produce meaningful results, possibly because this study was retrospective, the sample data may be biased, and larger sample sizes are needed to explore prognostic factors (*Table 2*).

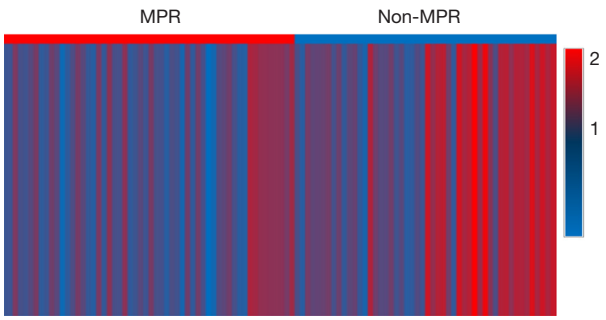
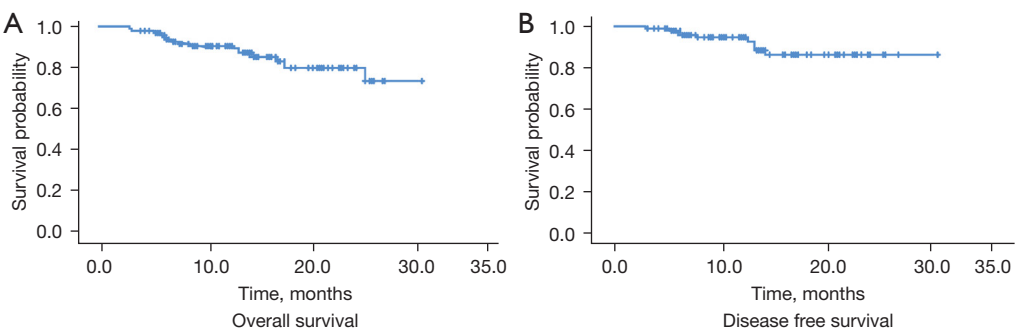


Figure 2 Distribution of ΔNLR in MPR group and non-MPR group patients. The right-hand legend indicates the multiplicity of change for ΔNLR. ΔNLR was defined as the ratio of the last NLR before surgery to the NLR before neoadjuvant therapy. MPR, major pathologic response; NLR, neutrophil-to-lymphocyte ratio.

Safety and surgical complications

Neoadjuvant therapy-related adverse events in this study were divided into chemotherapy-related adverse events and immune-related adverse events (irAEs), which are summarized in *Table 3*. The most common grade 1 or 2 chemotherapy-related adverse events were low hemoglobin (53/122, 43.4%), leukopenia (50/122, 41.0%), elevated aminotransferases (41/122, 33.6%), and thrombocytopenia (26/122, 21.3%). The most common grade 3 or 4 chemotherapy-related adverse events were leukopenia (13/122, 10.7%), low hemoglobin (10/122, 8.2%), neutropenia (7/122, 5.7%), and elevated aminotransferases (7/122, 5.7%). A total of 42 patients (42/122, 34.4%) had irAEs, among which the most common grade 1 or 2 irAEs were skin rashes (15/122, 12.3%), cutaneous capillary proliferation (11/122, 9.0%), pneumonitis (8/122, 6.6%), diarrhea (6/122, 4.9%), hypothyroidism (5/122, 4.1%), and hyperthyroidism (2/122, 1.6%). The most common grade 3 or 4 irAEs were rash (2/122, 1.6%), pneumonia (2/122, 1.6%), and diarrhea (1/122, 0.8%). None of the patients in the studies stopped treatment or delayed surgery due to treatment-related adverse events (TRAEs).

In this study, 106 patients who underwent surgery experienced postoperative complications including pneumonitis in 27 cases (25.5%), vocal cord paralysis in 23 cases (21.7%), pleural effusion in 16 cases (15.1%), gastrointestinal reactions in nine cases (8.5%), esophageal



Time, months	12	24
Survival probability, %	90.8	81.0

Time, months	12	24
Survival probability, %	94.4	86.0

Figure 3 Kaplan-Meier curves of overall patient overall survival and disease-free survival of surgical patients. (A) Overall survival of 122 patients. (B) Disease-free survival in 106 surgical patients.

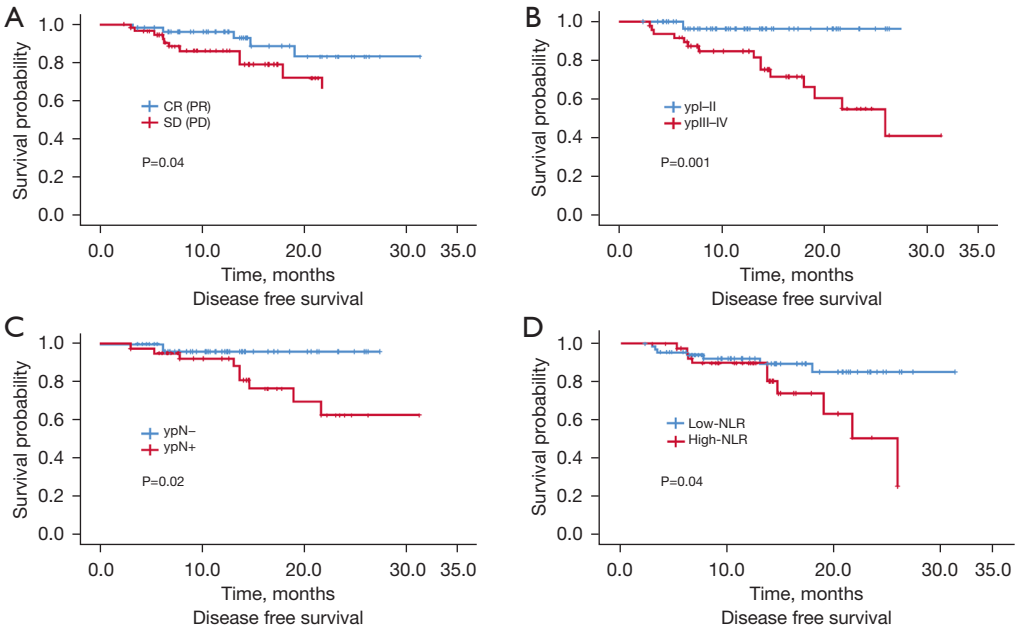


Figure 4 Kaplan-Meier curves of disease-free survival in different groups. (A) Disease-free survival for CR (PR) and SD (PD) patients. (B) Disease-free survival for ypI–II and ypIII–IV patients. (C) Disease-free survival for ypN– and ypN+ patients. (D) Disease-free survival for low-NLR and high-NLR patients. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NLR, neutrophil-to-lymphocyte ratio.

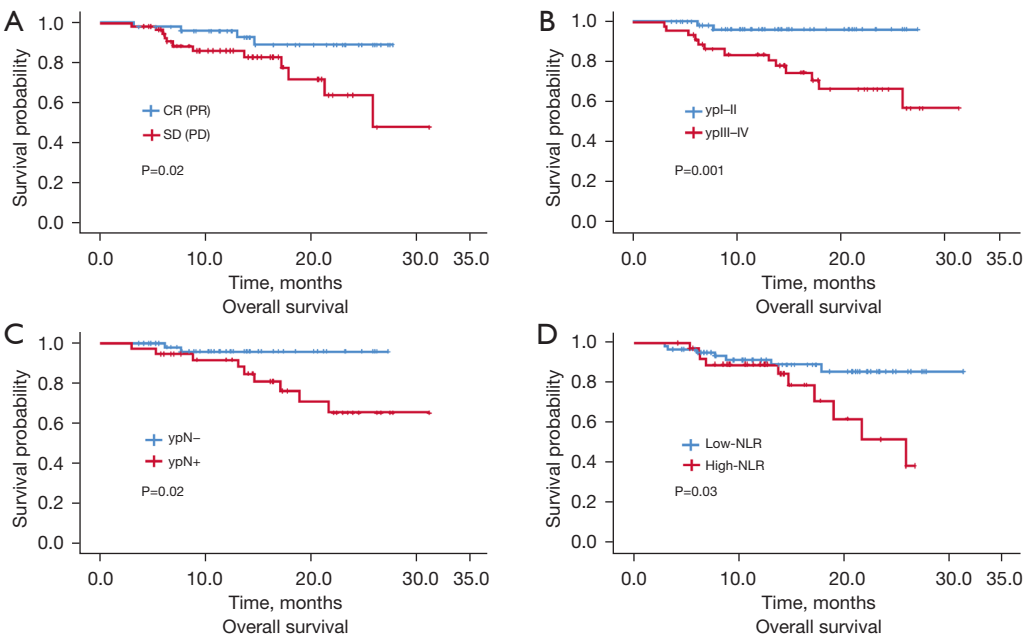


Figure 5 Kaplan-Meier curves of overall survival of patients in different groups. (A) Overall survival for CR (PR) and SD (PD) patients. (B) Overall survival for ypI–II and ypIII–IV patients. (C) Overall survival for ypN– and ypN+ patients. (D) Overall survival for low-NLR and high-NLR patients. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NLR, neutrophil-to-lymphocyte ratio.

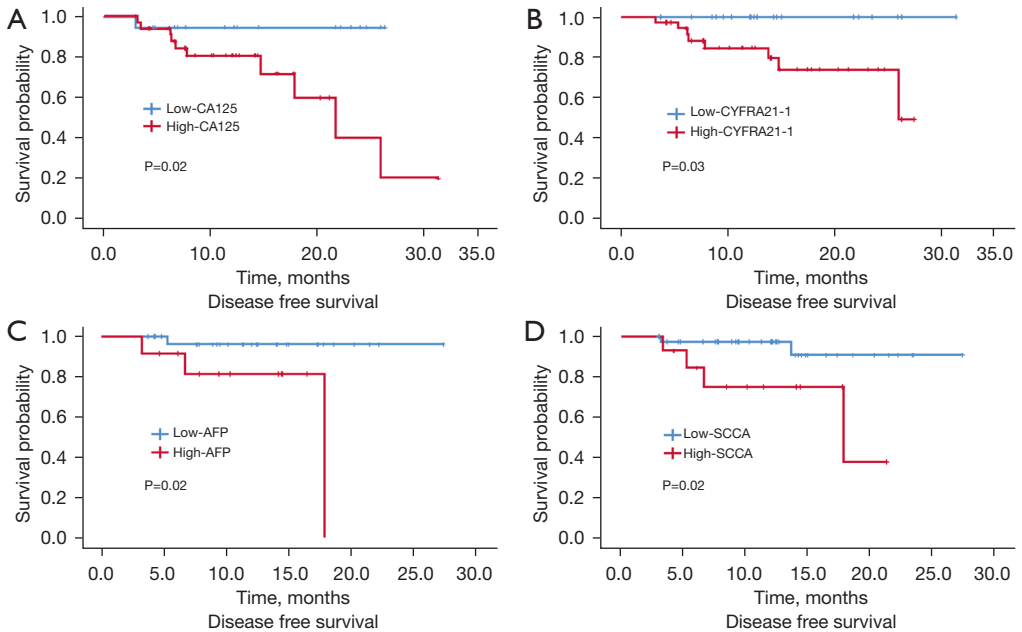


Figure 6 Kaplan-Meier curves of disease-free survival in different tumor marker groups. (A) Disease-free survival for low-CA125 and high-CA125 patients. (B) Disease-free survival for low-CYFRA21-1 and high-CYFRA21-1 patients. (C) Disease-free survival for low-AFP and high-AFP patients. (D) Disease-free survival for low-SCCA and high-SCCA patients. Tumor markers are all indicators of patients before neoadjuvant therapy. CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; AFP, alpha fetoprotein; SCCA, squamous cell carcinoma antigen.

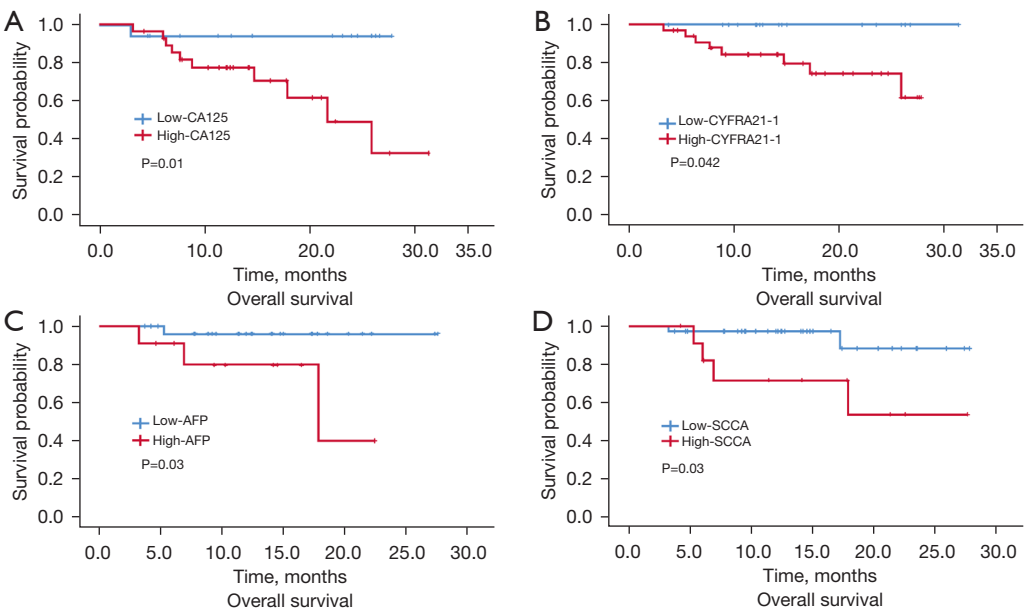


Figure 7 Kaplan-Meier curves of overall survival in different tumor marker groups. (A) Overall survival for low-CA125 and high-CA125 patients. (B) Overall survival for low-CYFRA21-1 and high-CYFRA21-1 patients. (C) Overall survival for low-AFP and high-AFP patients. (D) Overall survival for low-SCCA and high-SCCA patients. Tumor markers are all indicators of patients before neoadjuvant therapy. CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; AFP, alpha fetoprotein; SCCA, squamous cell carcinoma antigen.

Table 2 Univariate and multivariate analysis of OS and DFS for ESCC patients treated with neoadjuvant therapy

Characteristics	DFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age: <65 *vs*. ≥65 years	0.926 (0.356–2.407)	0.88	–	–	0.901 (0.325–2.500)	0.84	–	–
Gender: male *vs*. female	25.871 (0.018–37,448.356)	0.38	–	–	25.310 (0.014–45,835.042)	0.40	–	–
Smoking history: yes *vs*. no	3.450 (0.788–15.105)	0.10	–	–	3.080 (0.694–13.667)	0.14	–	–
Drinking history: yes *vs*. no	2.042 (0.748–5.577)	0.16	–	–	1.991 (0.679–5.843)	0.21	–	–
Tumor location: upper *vs*. middle/lower	0.788 (0.102–6.075)	0.82	–	–	0.721 (0.093–5.561)	0.75	–	–
Clinical stage: II *vs*. III–IV	0.514 (0.187–1.412)	0.20	–	–	0.539 (0.182–1.599)	0.27	–	–
ypTNM stage: I–II *vs*. III–IV	0.337 (0.161–0.706)	0.004	0.634 (0.065–6.181)	0.695	0.115 (0.0261–0.503)	0.004	0.568 (0.056–5.719)	0.63
Differentiation: poorly *vs*. well-moderately	1.182 (0.336–4.152)	0.80	–	–	1.086 (0.245–4.827)	0.91	–	–
ypT stage: ypT3–4 *vs*. ypT0–2	1.001 (0.265–3.779)	>0.99	–	–	1.457 (0.361–5.882)	0.60	–	–
ypN stage: ypN– *vs*. ypN+	0.198 (0.043–0.920)	0.04	0.758 (0.230–2.500)	0.65	0.201 (0.043–0.936)	0.041	0.687 (0.207–2.276)	0.54
NLR: low-NLR *vs*. high-NLR	0.609 (0.375–0.991)	0.046	1.444 (0.212–9.822)	0.71	0.358 (0.136–0.948)	0.04	1.118 (0.171–7.322)	0.91
CA125: low-CA125 *vs*. high-CA125	0.115 (0.014–0.931)	0.043	0.184 (0.017–2.000)	0.16	0.111 (0.014–0.891)	0.04	0.225 (0.023–2.184)	0.20
SCCA: low-SCCA *vs*. high-SCCA	0.168 (0.031–0.922)	0.040	0.281 (0.018–4.489)	0.37	0.177 (0.032–0.974)	0.047	0.322 (0.020–5.179)	0.42

OS, overall survival; DFS, disease-free survival; ESCC, esophageal squamous cell carcinoma; HR, hazard ratio; CI, confidence interval; TNM, tumor-node-metastasis; NLR, neutrophil-to-lymphocyte ratio; CA125, carbohydrate antigen 125; SCCA, squamous cell carcinoma antigen.

Table 3 Treatment-related AEs

Event	Grade 1–2, n (%)	Grade 3–4, n (%)
Chemotherapy-related adverse events (n=122)		
Myelosuppression		
Leukopenia	50 (41.0)	13 (10.7)
Low hemoglobin	53 (43.4)	10 (8.2)
Thrombocytopenia	26 (21.3)	2 (1.6)
Neutropenia	15 (12.3)	7 (5.7)
Transaminase elevation	41 (33.6)	7 (5.7)
Creatinine elevation	6 (4.9)	0 (0.0)
Hyperbilirubinemia	8 (6.6)	3 (2.5)
irAEs (n=122)		
Skin rashes	15 (12.3)	2 (1.6)
Cutaneous capillary proliferation	11 (9.0)	0 (0.0)
Pneumonitis	8 (6.6)	2 (1.6)
Diarrhea	6 (4.9)	1 (0.8)
Hypothyroidism	5 (4.1)	0 (0.0)
Hyperthyroidism	2 (1.6)	0 (0.0)

AEs, adverse events; irAEs, immune-related adverse events.

anastomotic stenosis in eight cases (7.5%), anastomotic leakage in five cases (4.7%), and bleeding in three cases (2.8%). Nine patients were readmitted to the hospital within 30 days after surgery, and the main reason for readmission was pneumonitis. One patient died of bleeding and multi-organ failure within 30 days after surgery. Summary of postoperative complications is shown in *Table 4*.

Discussion

In this study, we reported the use of neoadjuvant immunotherapy in locally advanced resectable esophageal cancer, and the results of a retrospective study of 122 patients who received nICT showed that the pCR rate (28/106, 26.4%) and MPR rate were acceptable (37/106, 34.9%). There was a near-perfect R0 resection rate (105/106, 99%). Patients with locally advanced ESCC undergoing nICT experienced neoadjuvant TRAEs and postoperative complications at levels deemed acceptable, and there were no delays in the surgical procedures.

There has been controversy about the treatment modalities of neoadjuvant therapy for esophageal cancer, including neoadjuvant chemotherapy, nCRT, and

Table 4 Postoperative complications (n=106)

Event	Any grade, n (%)
Pneumonitis	27 (25.5)
Vocal cord paralysis	23 (21.7)
Pleural effusion	16 (15.1)
Gastrointestinal reaction	9 (8.5)
Anastomotic stricture	8 (7.5)
Anastomotic leakage	5 (4.7)
Bleeding	3 (2.8)
30-day readmission to hospital	9 (8.5)
30-day mortality	1 (0.9)

neoadjuvant immunotherapy. There is no clear evidence that neoadjuvant therapy for locally advanced resectable ESCC is the most appropriate modality. Research indicates that achieving pCR and MPR is linked to improved OS and extended median disease-free survival (DFS) not only in esophageal cancer but also in various other cancer types. Consequently, the evaluation of neoadjuvant therapy efficacy can utilize the attainment of pCR and MPR as significant endpoints (20). Previous studies have shown that the pCR rate of patients with ESCC after neoadjuvant chemotherapy (nCT) treatment ranges from 3.8% to 10.7% (21,22), which is significantly lower than the pCR rate of 26.4% in this study. JCOG1109 compared the doublet and triplet of chemotherapy and chemoradiotherapy as neoadjuvant treatment. The results showed that the pCR rate in the DCF (docetaxel + cisplatin + 5-FU) group was significantly higher than that in the CF (cisplatin + 5-FU) group (2.1% *vs.* 19.8%). The R0 resection rate in the DCF group was higher than that in the CF group (84.4% *vs.* 85.6%). The study results indicated that both the CF group and the DCF group had lower pCR rates and R0 resection rates than those reported in this study (23). Han *et al.* conducted a meta-analysis of nCRT and neoadjuvant chemotherapy for esophageal cancer, and the results showed that the pCR rate in the nCRT group was significantly higher than that in the nCT group (21.6% *vs.* 5.7%), and both were lower than the pCR rate reported in this study (26.4%) (24). Zhao *et al.* showed that the R0 resection rate was 89.1% in the nCRT group, which was lower than the R0 resection rate of 99% in this study, and the pCR rate in the nCRT group was 23.63%, which was lower than the pCR rate of 26.4% in this study (25).

As immunotherapy becomes increasingly prevalent in the treatment of esophageal cancer, investigations into the potential of neoadjuvant immunotherapy for this condition are actively underway. In a recent investigation focusing on immune monotherapy for locally advanced resectable ESCC, the findings indicated an 8% rate of pCR and a 24% rate of MPR (26), which were lower than the pCR rate (8% *vs.* 26.4%) and MPR rate (24% *vs.* 34.9%) in this study. The NICE study (27) and the SIN-ICE study (28) were both neoadjuvant immunotherapy studies for esophageal cancer, and the results showed that the pCR rate and MPR rate were acceptable, which were similar to those in this study. Previous studies of neoadjuvant immunotherapy in combination with chemotherapy have shown a pCR rate of 25–33%, similar to the pCR rate in this study (9,29). The above-mentioned research results on neoadjuvant immunotherapy for esophageal cancer are similar to the findings of our study, both demonstrating a reasonable efficacy of neoadjuvant immunotherapy for esophageal cancer. This may be associated with the synergistic effects of immunotherapy and chemotherapy. Immunotherapy may be more effective in the preoperative neoadjuvant therapy phase, probably because in the early stages of the disease, immune cells are less likely to be depleted and patients with esophageal cancer respond better to immunotherapy, so early application of immunotherapy is expected to yield superior therapeutic outcomes for patients with locally advanced esophageal cancer (30).

Neoadjuvant therapy-related adverse events were common in this study, with a total of 93 patients experiencing any grade of TRAEs (93/122, 76.2%), of which 26 patients had grade 3–4 TRAEs (26/122, 21.3%), the most common was leukopenia (51.6%), and no patients delayed surgical treatment or death due to TRAEs. This study had shown superiority over other neoadjuvant immunotherapy studies for esophageal cancer on TRAEs. The KEEP-GO3 study recorded 100% incidence of any TRAEs, with leukopenia being the most common (76.7%), and grade 3–4 TRAEs occurring in 36.7% (31). In terms of surgical safety, no patients were delayed due to adverse effects of treatment, and the R0 resection rate was 99%, compared with 98% and 60% in previous nCRT and neoadjuvant chemotherapy studies (3,5). A total of 47 patients (47/122, 38.5%) developed surgery-related complications in this study. Pneumonia emerged as the predominant postoperative complication, occurring at a rate of 25.5%, which was comparatively lower than the reported range of 30% to 46% in studies involving nCRT (32). An investigation into the combination of neoadjuvant

immunotherapy and chemotherapy for esophageal cancer reveals that 47.1% of patients experienced surgery-related complications, and the incidence of pulmonary complications, including pneumonia, was 27.4%, both of which were inferior to the results of this study (33). The findings imply that the combined use of neoadjuvant immunotherapy and chemotherapy is associated with a favorable safety profile.

Inflammation has been shown to be closely associated with tumor progression, systemic inflammatory responses can predispose tumors to progression by promoting angiogenesis, inhibiting apoptosis, and DNA damage (34). The NLR revealed patient's inflammatory profile and immune status, which reflect changes in the tumor microenvironment (35). Multiple studies have shown that NLR is associated with the prognosis of a variety of cancers, including esophageal cancer (36-39). A meta-analysis exploring the correlation between the dynamic trend of NLR and the clinical effectiveness in cancer patients undergoing immunotherapy indicated that an upward trajectory in NLR post-immunotherapy was linked to an unfavorable clinical prognosis. Conversely, a decreasing trend in NLR was associated with an improved clinical prognosis (40). The prognostic analysis of this study suggested that NLR was associated with OS and DFS in neoadjuvant immunotherapy for esophageal cancer, and the results showed that low NLR had a better prognosis. Studies have shown that multiple tumor markers, such as CYFRA21-1, carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and SCCA, often predict prognosis in a variety of cancers, including esophageal cancer (41,42). In this study, Kaplan-Meier survival analysis and Cox univariate analysis of tumor markers showed that low CA125 and low SCCA had better prognosis.

There are some limitations to this study. First, this study is a single-arm single-center retrospective study. Second, some patients did not undergo surgery due to disease progression or personal reasons, so there may be some bias in the selection of patients for enrollment. Third, the follow-up period was limited, and we have not yet reached the median survival, highlighting the need for an extended, prolonged follow-up to thoroughly assess both the effectiveness and safety of nICT.

Conclusions

In summary, nICT is safe and feasible as a neoadjuvant treatment regimen for patients with locally advanced ESCC, with high R0 resection rate, satisfactory pCR rate and MPR rate, and controllable postoperative morbidity and mortality. However, the long-term survival effectiveness and safety of nICT still need to be verified by further research.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-169/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-169/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Affiliated Hospital, Nanchang University (No. IIT-2023335). Individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 The relationship between neoadjuvant treatment cycle, NLR before neoadjuvant therapy, last NLR before surgery, and Δ-NLR and MPR

Variables	Total (n=106)	MPR (n=65)	Non-MPR (n=41)	P
Neoadjuvant therapy cycle, n (%)				0.81
2	89 (84.0)	54 (60.7)	35 (39.3)	
>2	17 (16.0)	11 (64.7)	6 (35.3)	
NLR before neoadjuvant therapy (median)	–	2.62	2.90	0.66
Last NLR before surgery (median)	–	1.74	2.47	0.003
Δ-NLR, n (%)				0.001
<1	74 (69.8)	55 (74.3)	19 (25.7)	
≥1	32 (30.2)	10 (31.3)	22 (68.7)	

ΔNLR was defined as the ratio of the last NLR before surgery to the NLR before neoadjuvant therapy. NLR, neutrophil-to-lymphocyte ratio; MPR, major pathologic response.

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