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Survival and Perioperative Outcomes After Addition of Immunotherapy to Neoadjuvant Chemoradiotherapy for the Treatment of Locally Advanced Esophageal Squamous Cell Carcinoma

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ABSTRACT

Background: Currently, neoadjuvant chemoradiotherapy combined with immunotherapy (NCRI) for patients with locally advanced esophageal squamous cell carcinoma (ESCC) is attracting attention. The purpose of this study was to compare the surgical outcomes and survival between patients receiving NCRI and neoadjuvant chemoradiotherapy (NCRT) followed by surgery.

Methods: This study retrospectively included patients with locally advanced ESCC and treated with NCRI or NCRT followed by esophagectomy. Two groups were compared for pathologic complete response (pCR) rate, R0 resection rate, and 3-year recurrence-free survival (RFS). Surgery time, the number of lymph nodes removed, postoperative complications, and 30-day mortality were also compared. Propensity score matching (PSM) was performed to minimize the potential impact of confounding factors.

Results: After PSM, patients in the NCRI group showed a significantly higher pCR rate compared with those in the NCRT group (54.2% vs. 27.1%, $p=0.046$). R0 resection rate (100% vs. 89.6%, $p=0.251$), surgery time ($p=0.614$), the number of lymph nodes removed ($p=0.526$), the incidence of total postoperative complications (46.4% vs. 37.9%, $p=0.564$) and 30-day mortality (3.6% vs. 1.1%, $p=0.983$) were comparable between the two groups. The NCRI group exhibited a significantly higher 3-year RFS rate compared to the NCRT group (79.2% vs. 62.5%, $p=0.032$).

Conclusion: For patients with locally advanced ESCC, NCRI showed a significantly higher pCR rate than conventional NCRT, without increased operative risk. NCRI followed by surgery exhibited a superior RFS compared to NCRT followed by surgery. Prospective studies are needed in the future.

1 | Introduction

Esophageal cancer (EC) is the sixth most common cause of cancer-related mortality worldwide [1]. And esophageal squamous cell carcinoma (ESCC) is the main histological subtype, especially in Asians [2, 3]. Currently, neoadjuvant chemoradiotherapy (NCRT) followed by surgery has been considered the standard management for patients with locally advanced,

surgically resectable ESCC [4]. However, due to the high incidence of local recurrence and distant metastasis, nearly half of patients experience tumor progression and death within 5 years after NCRT followed by surgery [5–7]. The CROSS trial showed that the recurrence rate in the NCRT group was 35% after a median follow-up of 45 months [8]. A multicenter phase III trial (NEOCRTEC5010) reported that the pathologic complete response (pCR) rate was 43.2% in the NCRT group, and that 33.7% of patients with ESCC experienced recurrences after a median follow-up of 51.9 months [6]. In fact, limited progress has been made in the treatment of patients with locally advanced EC since preoperative chemoradiotherapy was first reported in 2012 [9, 10]. Therefore, a more powerful systemic therapeutic strategy is required to achieve a more promising outcome.

Recent breakthrough results from immune checkpoint inhibitors (ICIs), such as anti-programmed death 1 (PD-1) antibody, have paved the way for a new era of tumor immunotherapy [11, 12]. Multiple clinical trials have confirmed that ICIs combined with chemoradiotherapy or chemotherapy have a promising efficacy in the treatment of advanced or metastatic ESCC [13, 14]. Currently, neoadjuvant immunotherapy combined with chemoradiotherapy for patients with locally advanced ESCC is attracting attention. Certain satisfactory outcomes from neoadjuvant chemoradiotherapy combined with immunotherapy (NCRI) in locally advanced ESCC have been reported by some single-arm trials [10, 15, 16]. The PALACE-1 trial showed that NCRI was safe, did not delay surgery, and induced a pCR of 55.6% [15]. Even though the number of indications and patients in trials who were treated with NCRI has increased, perioperative safety and postoperative adverse events have not been adequately addressed. Especially, esophagectomy is an invasive treatment with a high incidence of postoperative complications and mortalities.

To date, there are few previous studies comparing the therapeutic response and surgical outcomes of NACI followed by surgery and NCRT [10, 16]. Therefore, the purpose of this retrospective study was to compare the pathological response, postoperative complications, and survival between locally advanced ESCC patients receiving NCRI followed by surgery and NCRT followed by surgery. In addition, propensity score matching (PSM) was performed to reduce bias caused by potential confounding factors.

2 | Patients and Methods

2.1 | Patients

This study retrospectively included patients with locally advanced ESCC and treated with NCRI or NCRT followed by esophagectomy from January 2021 to March 2022. Our study was conducted according to the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of the National Cancer Center, with obtaining informed consents. Eligible candidates were aged 18 years or older with pathologically confirmed ESCC and deemed to be surgically resectable (clinically staged as c T1N1-3M0 or T2-4aN0-3M0) by the multidisciplinary clinical team. Patients were excluded from the analysis if they were diagnosed as cervical EC or gastroesophageal junction cancer, or other histological subtypes, such as adenocarcinoma and neuroendocrine cancer, or with previous cancer or other concurrent cancers, or missing clinical data and follow-up data. A total of 115 eligible patients identified from the Chinese National Cancer Center/Cancer Hospital were included in our study. Among them, patients who received conventional NCRT were assigned as the NCRT group, whereas patients who received NCRI were assigned as the NCRI group.

All patients had clinical staging before neoadjuvant treatment, including endoscopy (ultrasound endoscopy) and biopsy, contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI), and positron emission tomography with integrated computed tomography (PET-CT) at baseline. Clinicopathologic staging was evaluated using the 8th edition American Joint Committee on Cancer (AJCC)/Union for International Cancer Control staging system [4]. After neoadjuvant treatment, the same standardized examinations as before were performed, but ultrasound endoscopy and biopsy were not necessary.

2.2 | Neoadjuvant Therapy and Surgery

All patients included in this study received neoadjuvant concurrent chemoradiotherapy. The radiotherapy regimen comprised a total radiation dose of 45–50.4 Gy, at 1.8–2.14 Gy per fraction daily. Radiotherapy techniques included three-dimensional conformal radiation (3D-CRT), intensity-modulated radiation therapy (IMRT) or volumetric intensity-modulated arc therapy (VMAT). Every patient received two to four courses of chemotherapy, and the regimen of chemotherapy mainly consisted of double or triplet drugs: platinum-based drugs (cisplatin or nedaplatin), taxel (docetaxel or paclitaxel) and 5-fluorouracil. Patients in the NACI group received at least two courses of ICIs concurrently with chemoradiotherapy, and the immunotherapy regimens mainly consisted of camrelizumab, sintilimab, or pembrolizumab (200 mg every 3 weeks). The dosage and usage of neoadjuvant treatment were determined by experienced physicians based on the condition and body surface area of each patient. Four to eight weeks after completion of neoadjuvant therapy, the patients underwent surgery. The standard surgical procedure was transthoracic McKeown minimally invasive esophagectomy (MIE) combined with 2-field or 3-field lymphadenectomy.

2.3 | Histopathology

Histopathologic specimens of each patient were carefully examined by two experienced pathologists, mainly focusing on pathological type, resection margins, tumor regression characteristics, and treatment response. The pathological staging was assessed according to the latest edition of the AJCC staging system (8th edition) [4]. The primary endpoint was pCR rate, and the pCR was defined as no evidence of residual vital tumor cells in the primary tumor area and all resected lymph nodes. R0 resection was defined as curative resection with a negative resection margin (the distal, proximal, or circumferential resection margin), and microscopically incomplete resection was recorded as incomplete resection (R1) [17]. The degree of tumor regression after preoperative therapy was quantified using the Mandard tumor regression grade (TRG) scoring system [17, 18].

2.4 | Postoperative Outcomes and Survival

Postoperative complications after surgery were diagnosed according to the Esophageal Complications Consensus Group (ECCG) criteria [19]. Pulmonary complications included pneumonia, pleural effusion, pneumothorax, atelectasis, and respiratory failure requiring reintubation. Cardiac complications included arrhythmia, pericardial effusion, and heart failure. The severity of complications was assessed according to the Clavien-Dindo classification [20]. Major complications were defined as grade ≥ 3, in accordance with the Clavien-Dindo classification system. Intensive care unit (ICU) readmission, In-hospital mortality, and 30-day mortality after surgery were compared between the two groups. Postoperative 30-day mortality was defined as death occurring during the first 30 days after surgery. The recurrence-free survival (RFS) was defined as the interval between the time of surgery and the time of tumor recurrence or death or the last follow-up. The overall survival (OS) refers to the duration, measured in months, between the surgical procedure and either the date of mortality or the most recent follow-up.

2.5 | Statistical Analysis

Statistical analyses were performed using the R statistical software for Windows (version 4.0.0, https://cran.R-project.org) and the SPSS software (version 24.0, IBM Corp., Armonk, NY). The mean and standard deviation were used for descriptive continuous variables and categorical variables were presented as frequencies and percentages. Data from two groups of patients were compared by the Kruskal–Wallis test or independent *t*-test for continuous variables according to the normality of the data and by the χ^2 test or Fisher's exact test for categorical variables as appropriate. Propensity score analysis (PSM) was designed to eliminate selection bias due to measured confounders [21, 22]. A propensity score for each patient was accounted using a logistic regression model in which variables of age, sex, smoking index, comorbidities, Karnofsky performance score, tumor length, tumor location and clinical staging. Patients from the NCRI group and the NCRT group were matched (1:2) according to nearest-neighbor matching on the logit scale without replacement. Subgroup analyses based on PSM were performed. PSM analyses were conducted using R software, and the "MatchIt" package is applied for the matching procedure. The researchers performed survival studies by using Kaplan–Meier curves and performed the log-rank test for comparison. RFS analyses were performed in patients with R0 resection. Survival analyses were conducted before and after PSM. A two-sided p value <0.05 was considered as statistically significant difference for all analyses.

3 | Results

3.1 | Patient Characteristics

Among 115 patients with locally advanced ESCC, 87 patients received conventional NCRT (the NCRT group), whereas 28 patients received NCRI (the NCRI group), as shown in Figure 1. Basic characteristics of patients in the two groups are described in Table 1. To reduce the effect of confounding bias, a PSM method was used between the NCRI group ($n=24$) and the NCRT group ($n=48$). After PSM, the clinical characteristics of patients in the two subgroups were well balanced, as summarized in Table 1.

3.2 | Surgery and Pathological Examination

In terms of surgery-related outcomes shown in Table 2, there were not significant differences in surgery time ($p=0.328$), R0 resection rate ($p=0.384$), number of lymph nodes removed ($p=0.665$) and positive lymph nodes ($p=0.517$) between the

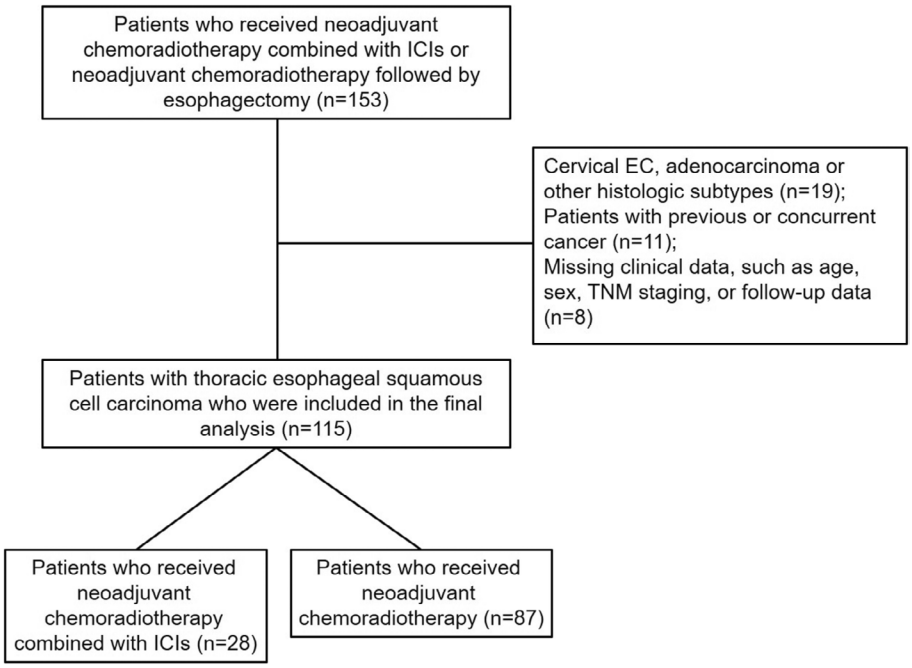

FIGURE 1 | Patient selection diagram.

TABLE 1 | Baseline characteristics of all patients in two groups before and after PSM.

		Before PSM			After PSM		
Variables	**Total ($n=115$)**	**NCRT ($n=87$)**	**NCRI ($n=28$)**	***p***	**NCRT ($n=48$)**	**NCRI ($n=24$)**	***p***
Age, *n* (%)							
≤60	60 (52.2)	46 (52.9)	14 (50.0)	0.962	19 (39.6)	11 (45.8)	0.800
>60	55 (47.8)	41 (47.1)	14 (50.0)		29 (60.4)	13 (54.2)	
Sex, *n* (%)							
Male	96 (83.5)	73 (83.9)	23 (82.1)	0.778	41 (85.4)	19 (79.2)	0.737
Female	19 (16.5)	14 (16.1)	5 (17.9)		7 (14.6)	5 (20.8)	
Smoking index, *n* (%)							
<400	59 (51.3)	47 (54.0)	12 (42.9)	0.417	20 (41.7)	9 (37.5)	0.932
≥400	56 (48.7)	40 (46.0)	16 (57.1)		28 (58.3)	15 (62.5)	
Comorbidities, *n* (%)							
Yes	65 (56.5)	46 (52.9)	19 (67.9)	0.241	31 (64.6)	16 (66.7)	1.000
No	50 (43.5)	41 (47.1)	9 (32.1)		17 (35.4)	8 (33.3)	
Karnofsky performance score, *n* (%)							
90	88 (76.5)	65 (74.7)	23 (82.1)	0.582	38 (79.2)	20 (83.3)	0.916
100	27 (23.5)	22 (25.3)	5 (17.9)		10 (20.8)	4 (16.7)	
Length of tumor, *n* (%)							
≤5.0 cm	62 (53.9)	49 (56.3)	13 (46.4)	0.487	24 (50.0)	11 (45.8)	0.934
>5.0 cm	53 (46.1)	38 (43.7)	15 (53.6)		24 (50.0)	13 (54.2)	
Location of tumor, *n* (%)							
Upper	16 (13.9)	10 (11.5)	6 (21.4)	0.382	9 (18.8)	6 (25.0)	0.587
Middle	53 (46.1)	42 (48.3)	11 (39.3)		22 (45.8)	8 (33.3)	
Lower	46 (40.0)	35 (40.2)	11 (39.3)		17 (35.4)	10 (41.7)	
Clinical T stage, *n* (%)							
T2	9 (7.8)	7 (8.0)	2 (7.1)	1.000	5 (10.4)	2 (8.3)	0.961
T3	99 (86.1)	74 (85.1)	25 (89.3)		41 (85.4)	21 (87.5)	
T4a	7 (6.1)	6 (6.9)	1 (3.6)		2 (4.2)	1 (4.2)	
Clinical N stage, *n* (%)							
N0	15 (13.0)	11 (12.6)	4 (14.3)	0.040	9 (18.8)	4 (16.7)	0.246
N1	71 (61.7)	57 (65.5)	14 (50.0)		25 (52.1)	12 (50.0)	
N2	24 (20.9)	18 (20.7)	6 (21.4)		14 (29.2)	6 (25.0)	
N3	5 (4.3)	1 (1.1)	4 (14.3)		0 (0.0)	2 (8.3)	
Clinical TNM stage, *n* (%)							
II	23 (20.0)	17 (19.5)	6 (21.4)	0.212	14 (29.2)	6 (25.0)	0.418
III	81 (70.4)	64 (73.6)	17 (60.7)		32 (66.7)	15 (62.5)	
IVA	11 (9.6)	6 (6.9)	5 (17.9)		2 (4.2)	3 (12.5)	

two groups. After receiving neoadjuvant therapy, pathological T stage ($p=0.744$), N stage ($p=0.217$), TNM stage ($p=0.329$) and TRG score ($p=0.728$) were similar in both groups. Notably, there were 14 patients (14/28, 50.0%) in the NCRI group achieving pCR, and 31 patients (31/87, 35.6%) achieving pCR in the NCRT group. The pCR rate in the NCRI group was higher than that in the NCRT group, but differences were not statistically different ($p=0.257$, Table 2).

TABLE 2 | Operative outcomes and treatment response in both groups before and after PSM.

	Before PSM			After PSM		
Characteristics	**NCRT ($n=87$)**	**NCRI ($n=28$)**	***p***	**NCRT ($n=48$)**	**NCRI ($n=24$)**	***p***
Surgery time (mean (SD))						
	264.06 (71.81)	279.18 (67.53)	0.328	261.77 (73.94)	270.92 (68.69)	0.614
R0, *n* (%)						
R0	77 (88.5)	27 (96.4)	0.384	43 (89.6)	24 (100.0)	0.251
R1	10 (11.5)	1 (3.6)		5 (10.4)	0 (0.0)	
Number of lymph nodes removed (mean (SD))						
	33.16 (11.32)	32.07 (12.21)	0.665	34.31 (12.22)	32.33 (12.82)	0.526
Number of positive lymph nodes (mean (SD))						
	0.97 (2.07)	0.68 (1.91)	0.517	1.19 (2.56)	0.79 (2.04)	0.512
T stage, *n* (%)						
T0	36 (41.4)	14 (50.0)	0.744	18 (37.5)	13 (54.2)	0.640
T1a	3 (3.4)	1 (3.6)		3 (6.2)	1 (4.2)	
T1b	10 (11.5)	2 (7.1)		7 (14.6)	1 (4.2)	
T2	14 (16.1)	2 (7.1)		4 (8.3)	1 (4.2)	
T3	23 (26.4)	8 (28.6)		15 (31.2)	7 (29.2)	
T4a	1 (1.1)	1 (3.6)		1 (2.1)	1 (4.2)	
N stage, *n* (%)						
N0	57 (65.5)	23 (82.1)	0.217	28 (58.3)	19 (79.2)	0.234
N1	19 (21.8)	2 (7.1)		13 (27.1)	2 (8.3)	
N2	10 (11.5)	2 (7.1)		6 (12.5)	2 (8.3)	
N3	1 (1.1)	1 (3.6)		1 (2.1)	1 (4.2)	
TNM stage, *n* (%)						
I	46 (52.9)	18 (64.3)	0.329	21 (43.8)	15 (62.5)	0.309
II	10 (11.5)	4 (14.3)		6 (12.5)	3 (12.5)	
IIIA	9 (10.3)	0 (0.0)		6 (12.5)	0 (0.0)	
IIIB	21 (24.1)	5 (17.9)		14 (29.2)	5 (20.8)	
IVA	1 (1.1)	1 (3.6)		1 (2.1)	1 (4.2)	
TRG, *n* (%)						
TRG1	36 (41.4)	14 (50.0)	0.728	19 (39.6)	13 (54.2)	0.582
TRG2	20 (23.0)	5 (17.9)		11 (22.9)	4 (16.7)	
TRG3	14 (16.1)	6 (21.4)		8 (16.7)	5 (20.8)	
TRG4	16 (18.4)	3 (10.7)		9 (18.8)	2 (8.3)	
TRG5	1 (1.1)	0 (0.0)		1 (2.1)	0 (0.0)	
PCR, *n* (%)						
CR	31 (35.6)	14 (50.0)	0.257	13 (27.1)	13 (54.2)	0.046
Non-CR	56 (64.4)	14 (50.0)		35 (72.9)	11 (45.8)	

Abbreviations: PCR, pathologic complete response; TRG, tumor regression grade.

TABLE 3 | Postoperative complications and mortality in both groups before and after PSM.

Variables	Before PSM			After PSM		
	NCRT ($n=87$)	NCRI ($n=28$)	p	NCRT ($n=48$)	NCRI ($n=24$)	p
Total complications, *n* (%)						
No	54 (62.1)	15 (53.6)	0.564	30 (62.5)	13 (54.2)	0.671
Yes	33 (37.9)	13 (46.4)		18 (37.5)	11 (45.8)	
Major complications, *n* (%)						
No	74 (85.1)	22 (78.6)	0.609	40 (83.3)	19 (79.2)	0.914
Yes	13 (14.9)	6 (21.4)		8 (16.7)	5 (20.8)	
Pneumonia, *n* (%)						
No	75 (86.2)	24 (85.7)	1.000	42 (87.5)	20 (83.3)	0.904
Yes	12 (13.8)	4 (14.3)		6 (12.5)	4 (16.7)	
Pneumothorax, *n* (%)						
No	84 (96.6)	27 (96.4)	1.000	46 (95.8)	23 (95.8)	1.000
Yes	3 (3.4)	1 (3.6)		2 (4.2)	1 (4.2)	
Atelectasis, *n* (%)						
No	85 (97.7)	28 (100.0)	1.000	47 (97.9)	24 (100.0)	1.000
Yes	2 (2.3)	0 (0.0)		1 (2.1)	0 (0.0)	
Pleural effusions, *n* (%)						
No	77 (88.5)	23 (82.1)	0.584	41 (85.4)	19 (79.2)	0.737
Yes	10 (11.5)	5 (17.9)		7 (14.6)	5 (20.8)	
Respiratory failure, *n* (%)						
No	83 (95.4)	26 (92.9)	0.970	47 (97.9)	22 (91.7)	0.532
Yes	4 (4.6)	2 (7.1)		1 (2.1)	2 (8.3)	
Anastomotic leak, *n* (%)						
No	85 (97.7)	26 (92.9)	0.533	46 (95.8)	23 (95.8)	1.000
Yes	2 (2.3)	2 (7.1)		2 (4.2)	1 (4.2)	
RLN injury, *n* (%)						
No	83 (95.4)	27 (96.4)	1.000	47 (97.9)	23 (95.8)	1.000
Yes	4 (4.6)	1 (3.6)		1 (2.1)	1 (4.2)	
Cardiac complications, *n* (%)						
No	86 (98.9)	26 (92.9)	0.294	47 (97.9)	23 (95.8)	1.000
Yes	1 (1.1)	2 (7.1)		1 (2.1)	1 (4.2)	
Other complications, *n* (%)						
No	80 (92.0)	25 (89.3)	0.960	43 (89.6)	21 (87.5)	1.000
Yes	7 (8.0)	3 (10.7)		5 (10.4)	3 (12.5)	
Clavien-Dindo grade, *n* (%)						
I	8 (24.2)	3 (23.1)	0.770	4 (22.2)	2 (18.2)	0.580
II	12 (36.4)	4 (30.8)		6 (33.3)	4 (36.4)	
III	8 (24.2)	4 (30.8)		7 (38.9)	3 (27.3)	

(Continues)

TABLE 3 | (Continued)

Variables	Before PSM			After PSM		
	NCRT ($n=87$)	NCRI ($n=28$)	p	NCRT ($n=48$)	NCRI ($n=24$)	p
IV	4 (12.1)	1 (7.7)		1 (5.6)	1 (9.1)	
V	1 (3.0)	1 (7.7)		0 (0.0)	1 (9.1)	
ICU readmission, *n* (%)						
No	79 (90.8)	25 (89.3)	1.000	45 (93.8)	21 (87.5)	0.651
Yes	8 (9.2)	3 (10.7)		3 (6.2)	3 (12.5)	
In-hospital mortality, *n* (%)						
No	87 (100.0)	28 (100.0)	1.000	48 (100.0)	24 (100.0)	1.000
Yes	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
30-Day mortality, *n* (%)						
No	86 (98.9)	27 (96.4)	0.983	48 (100.0)	23 (95.8)	0.722
Yes	1 (1.1)	1 (3.6)		0 (0.0)	1 (4.2)	

Abbreviations: ICU, intensive care unit; RLN, recurrent laryngeal nerve.

After PSM, surgery time ($p=0.614$, Table 3), R0 resection rate ($p=0.251$), number of lymph nodes removed ($p=0.526$) and positive lymph nodes ($p=0.512$), T stage ($p=0.640$), N stage ($p=0.234$), TNM stage ($p=0.309$) and TRG score ($p=0.582$) were comparable between the two groups. However, patients in the NCRI group showed a significantly higher pCR rate compared with those in the NCRT group (54.2% vs. 27.1%, $p=0.046$, Table 2).

3.3 | Postoperative Complications and Mortality

Postoperative complications and mortality in both groups were summarized in Table 3. During the postoperative periods, the most common complications in the NCRI group were pneumonia ($n=4$, 14.3%), pleural effusions ($n=5$, 17.9%), pneumothorax ($n=1$, 3.6%), respiratory failure ($n=2$, 7.1%), anastomotic leakage ($n=2$, 7.1%), recurrent laryngeal nerve (RLN) injury ($n=1$, 3.6%) and cardiac complications ($n=2$, 7.1%). The incidence of total postoperative complications (46.4% vs. 37.9%, $p=0.564$) and major complications (21.4% vs. 14.9%, $p=0.609$) was comparable between the two groups. In addition, there were no significant differences in ICU readmission (10.7% vs. 9.2%, $p=1.000$) and 30-day mortality (3.6% vs. 1.1%, $p=0.983$) between the two groups. After PSM, similar results were observed as shown in Table 3.

3.4 | Survival

The complete cohort was followed up until September 30, 2024, with a median duration of 36 months and a quartile range spanning from 32 to 43 months. As depicted in Figure 2A, the NCRI group had 1-year, 2-year, and 3-year RFS rates of 92.9%, 85.7%, and 78.6%, respectively, whereas the NCRT group displayed rates of 77.0%, 65.5%, and 61.5%, respectively. Remarkably enhanced RFS was observed in the NCRI group, which was statistically significant ($p=0.036$). The NCRI group had 1-year, 2-year, and 3-year OS rates of 96.4%, 88.3%, and 80.1%, respectively, whereas the NCRT group displayed rates of 89.7%, 80.3%, and 75.7%, respectively. The OS rates in the NCRI group were found to be higher compared to those in the NCRT group. However, it is important to note that the observed difference did not reach statistical significance ($p=0.144$, Figure 2B).

After PSM, similar results were detected. NCRI also yielded a higher RFS rate compared to NCRT (2-year RFS rate: 87.5% vs. 66.7%, 3-year RFS rate: 79.2% vs. 62.5%, $p=0.032$, Figure S1A). The NCRI group exhibited greater OS rates compared to the NCRT group (2-year OS rate: 90.7% vs. 72.9%, 3-year OS rate: 83.3% vs. 70.7%). Nevertheless, the statistical analysis conducted did not reveal a statistically significant difference between the two groups ($p=0.105$, Figure S1B).

4 | Discussion

In this study, there were no significant differences in postoperative complications, major complications, ICU readmission, and 30-day mortality between the NCRI group and the NCRT group. Surgery time, R0 resection rate, and number of lymph nodes removed have shown no significant differences between the two groups. However, patients in the NCRI group showed a significantly higher pCR rate compared with those in the NCRT group after PSM. The NCRI group also showed a higher RFS rate compared to the NCRT.

R0 resection rates of patients with ESCC in the CROSS trial were 85.5% [23]. Our study showed an R0 resection rate of 88.5% in patients receiving NCRT, similar to the results in the CROSS trial. In addition, the R0 resection rate of patients who received NCRI was 96.4% in our study, which was not statistically higher than that of patients who received NCRT. However, immunotherapy combined with neoadjuvant chemoradiotherapy brought a better pCR rate in patients with locally advanced ESCC. Our study

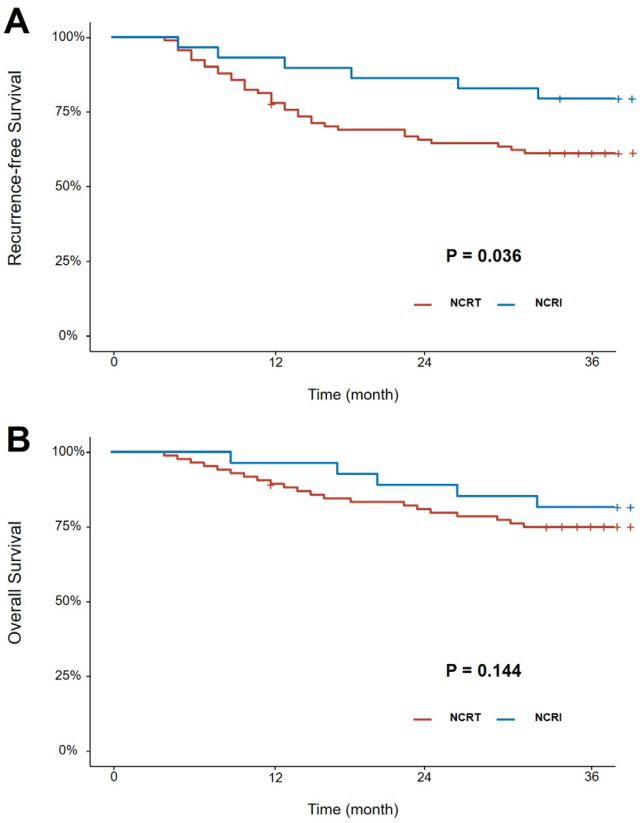

FIGURE 2 | (A) illustrates the comparison of RFS rates between two groups prior to PSM. (B) Comparison in the OS rates between two groups prior to PSM.

observed that the pCR rate of patients who received NCRI was 50.0%, similar to the PALACE-1 trial [15]. Patients receiving NCRI obtained a higher pCR rate compared with patients receiving NCRT, but there was no statistical difference. This may be influenced by some confounding factors. To reduce the effect of confounding bias, a PSM method was used. After PSM, patients in the NCRI group showed a significantly higher pCR rate compared with those in the NCRT group (54.2% vs. 27.1%, $p=0.046$). The reason for this exciting result may be that the addition of immunotherapy improves the short-term efficacy of NCRT. In addition, immunotherapy and radiotherapy and chemotherapy also have synergistic anti-tumor effects, resulting in better short-term results than single application [24–28].

There is concern that the addition of ICIs to neoadjuvant therapy will increase the difficulty of surgery or decrease the quality of lymph node dissection. However, in contrast to our initial assumption, our results showed that the addition of ICIs did not increase the difficulty and the time of surgery. The numbers of dissected lymph nodes were comparable between the two groups. These results implied that the addition of ICIs to preoperative therapy did not decrease the quality of radial esophagectomy. In addition, total postoperative complications, major complications, pulmonary complications, anastomotic leakage, and RLN injury developed similarly in both groups. Similar results were reported in previous studies [10, 16]. Sihag et al. [10] reported no statistical difference in operative mortality between the two groups. We also observed no significant difference in in-hospital mortality and 30-day postoperative mortality. On the basis of these results, esophagectomy following combined neoadjuvant immunotherapy and chemoradiotherapy appears to be safe and feasible for patients with locally advanced ESCC.

Currently, limited information on the survival rate has been published, so survival benefits have not been recognized by all clinical physicians. There is no difference in the 3-year OS rates (NCRT vs. NCT: 64.1% vs. 54.9%, $p=0.28$) between the two most commonly used neoadjuvant treatment regimens, with no difference in the RFS ($p=0.75$) [29]. The survival of new neoadjuvant therapy is worth exploring. Another study showed a better 3-year OS rate (91.7% vs. 79.8%; $p=0.032$) and a better 3-year DFS rate (87.4% vs. 72.8%; $p=0.039$) in patients who received neoadjuvant chemotherapy and ICIs, compared with those who received NCRT [30]. Our findings indicated that patients assigned to the NCRI group had significantly improved RFS compared to those in the NCRT group. Consistent results were observed after PSM adjustment. Perhaps it was related to the combination of NCRT and ICIs, which could enhance the pCR of tumors, inhibit recurrence and metastasis, thereby achieving durable tumor control and bestowing a prolonged RFS benefit. Although no statistical difference was detected in our study, the 3-year OS rate of patients who underwent NCRI was 80.1%, slightly higher than 75.7% of those who underwent NCRT. The duration of follow-up in our study was insufficient to reflect fully developed OS outcomes. Hence, more studies are needed to determine the extent of the survival advantage after NCRI and surgery in cases with locally advanced ESCC.

Our study has several limitations. First, it is a retrospective study with a relatively small sample size, and thus, statistical analysis may be underpowered. However, propensity score matching (PSM) was performed to reduce bias caused by potential confounding factors. Second, Differences in the drugs and doses of neoadjuvant chemotherapy and immunotherapy may affect the results of this study. Third, this study did not compare treatment-related adverse events during neoadjuvant therapy between the two groups. To overcome the limitations of our study, a randomized prospective study is needed in the future.

In conclusion, patients in the NCRI group showed a significantly higher pCR rate compared with those in the NCRT group after PSM. NCRI was significantly correlated to a better 3-year RFS in locally advanced ESCC patients than NCRT. R0 resection rate, surgery time, number of lymph nodes removed, and positive lymph nodes were comparable between the two groups. In addition, there were no significant differences in total postoperative complications, major complications, and operative mortality in both groups. Randomized studies with larger sample sizes of patients will be needed to confirm our results.

Author Contributions

Canjun Li: writing – review and editing, writing – original draft, formal analysis, investigating, and data curation. **Xin Wang:** writing – review and editing, resources, and data curation. **Lei Deng:** resources and data curation. **Jianyang Wang:** resources and data curation. **Tao Zhang:** resources and data curation. **Wenqing Wang:** resources and data curation. **Wenyang Liu:** resources and data curation. **Jima Lv:** resources and data curation. **Qinfu Feng:** resources and data curation. **Zongmei Zhou:** resources and data curation. **Xiankai Chen:** resources and data

curation. **Ruixiang Zhang:** resources, data curation. **Jianjun Qin:** resources and data curation. **Yin Li:** resources and data curation. **Nan Bi:** writing – review and editing, resources, Funding acquisition, data curation and conceptualization.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.