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Comparison of pathologic response and survival outcomes between neoadjuvant chemoradiotherapy (nCRT) and neoadjuvant immunochemotherapy (nICT) in patients with locally advanced esophageal squamous cell carcinoma: a propensity score-matched analysis

Yi Wang[1†], Ke Ma[2†], Huan Zhang[3†], Lei Wu[1], Li Liu[1], Yehan Zhou[4], Lin Peng[2], Qifeng Wang[1*†] and Xiang Zhuang[2,3*†]

Abstract

Background In locally advanced, operable esophageal squamous cell carcinoma (ESCC), neoadjuvant immunochemotherapy (nICT) has shown results that are somewhat comparable to those of standard neoadjuvant chemoradiotherapy (nCRT). The impact of these neoadjuvant treatments on survival outcomes, however, has yet to be elucidated.

Methods This study included 489 patients with locally advanced ESCC who underwent surgery at Sichuan Cancer Hospital after receiving neoadjuvant treatment between June 2017 and September 2023. Patients were categorized into nCRT and nICT groups based on whether they received neoadjuvant treatment. To mitigate potential biases and balance covariates between the two cohorts, 1:2 propensity score matching (PSM) was conducted using a caliper width of 0.05.

Results After PSM, the baseline characteristics of the 360 patients remained balanced between the two groups. The findings indicated a superior pathological response in the nCRT group, as evidenced by significantly greater rates of complete response (32.87% vs 14.58%, $P < 0.001$) and favorable tumor regression grade (TRG), as well as reduced ypT stages and less perineural and angioinvasion, despite comparable ypN stages. Despite the improvement

[†]Yi Wang, Ke Ma and Huan Zhang are co-first authors.

[†]Qifeng Wang and Xiang Zhuang contributed equally as joint senior authors.

*Correspondence:
Qifeng Wang
littlecancer@163.com
Xiang Zhuang
13882191333@139.com
Full list of author information is available at the end of the article

in complete pathological response (pCR) in the nCRT group, the 3-year disease-free survival (DFS) and overall survival (OS) rates did not significantly differ between the groups (DFS: 58.32% vs 56.16%, $P=0.67$; OS: 69.96% vs 71.99%, $P=0.99$). Crucially, The nICT group showed a lower incidence of grade 3 and 4 adverse events in Leukopenia (2.8% vs 29%; $P<0.001$) and Neutropenia (2.8% vs 24%; $P<0.001$) during neoadjuvant treatment, comparing with nCRT group.

Conclusions Our preliminary findings suggest that nICT followed by surgery offers comparable survival rates to nCRT, despite being less effective in pathologic outcomes. Nonetheless, nICT is a safe and feasible strategy for locally advanced ESCC, warranting further exploration to understand its impact on long-term survival.

Keywords Neoadjuvant immunochemotherapy, Neoadjuvant chemoradiotherapy, Locally advanced esophageal squamous cell carcinoma, Pathologic response, Propensity Score Matching (PSM)

Background

Esophageal carcinoma (EC) is an aggressive disease with a poor prognosis that affects millions of people worldwide [1, 2]. In China, EC ranks as the fourth leading cause of cancer-related deaths and the sixth most common cancer, with esophageal squamous cell carcinoma (ESCC) constituting more than 90% of EC cases [3, 4].

The efficacy of neoadjuvant chemoradiotherapy (nCRT) followed by surgery in improving outcomes for ESCC patients has been firmly established by pivotal studies, including the CROSS (Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study) and NEOCRTEC5010 trials [5, 6]. This regimen is recommended as the standard approach for managing locally advanced ESCC. However, the recurrence rate remains as high as 31–39% within 3–5 years after surgery for locally advanced ESCC patients [7, 8]. Thus, it is imperative to investigate more effective therapeutic modalities. In the wake of significant advancements in cancer immunotherapy, neoadjuvant immunochemotherapy (nICT) combined with surgery has emerged as a promising multidisciplinary approach aimed at enhancing long-term survival in ESCC patients. Recent single-arm studies have shown that the application of nICT in patients with locally advanced ESCC is both safe and efficient [9, 10]. Retrospective pilot studies also revealed that patients with locally advanced ESCC who underwent nICT followed by minimally invasive esophagectomy (MIE) had similar mortality and morbidity to those who underwent nCRT [11, 12]. However, the effectiveness of immunotherapy in locally advanced, resectable esophageal cancer remains controversial. Due to the small sample sizes in previous studies, the pathological complete response (pCR) rates following nICT lack reliable conclusions, ranging from 7% to 39.2% [9, 10, 13–15]. On the other hand, although these rates are slightly lower than those observed with nCRT [5, 6], the lack of direct comparisons with nCRT makes it difficult to determine the optimal neoadjuvant treatment strategy. Additionally, it remains unclear whether the differences in pathological response between these two neoadjuvant treatments translate into differences in long-term survival.

Hence, we conducted this retrospective study with large-cohort to further assess the pathological responses and survival of patients who underwent nICT or nCRT followed by surgery for locally advanced ESCC.

Methods

Patient selection

ESCC patients who received neoadjuvant immunochemotherapy (nICT) or neoadjuvant chemoradiotherapy (nCRT) following radical esophagectomy between June 2017 and September 2021 at Sichuan Cancer Hospital were retrospectively screened. Eligible participants were those diagnosed with ESCC who had undergone nICT or nCRT followed by esophagectomy. The inclusion criteria were a clinical stage of cT2 to cT4aN0 to N3 without evidence of metastatic disease (M0), as classified by the International Union Against Cancer Tumor, Node, Metastasis (TNM) Classification, 8th edition, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Exclusion criteria included patients who received a radiation dose exceeding 45 Gy or less than 36 Gy in the nCRT cohort. This study was approved by the ethics committee of our institution (ethical approval number SCCHEC-02–2023-029). Informed consent was waived by the ethics committee.

Neoadjuvant treatment and esophagectomy

All participants underwent 1 to 4 cycles of neoadjuvant chemotherapy. The chemotherapy protocols involved platinum-based drugs (e.g., cisplatin, carboplatin, or nedaplatin) plus paclitaxel or fluorouracil (with specific dosages and 3-week intervals). Additionally, patients in the nICT group received PD-1 inhibitors (toripalimab, camrelizumab, sintilimab, or pembrolizumab) in combination with chemotherapy. Patients initially treated with nICT were predominantly enrolled in a prospective trial (NCT04177797) [15]. The chemotherapy and immunotherapy regimen, including dosage and cycles, is decided

upon by the treating physician and patient based on the patient's physical state. For those in the nCRT group, most patients received involved-field irradiation (IFI), including any positive lymph nodes, while a small number of patients accepted elective nodal irradiation (ENI). The total dose ranged from 36 to 45 Gy, delivered in 1.8 to 2.0 Gy per fraction, over 20 to 25 fractions, with 5 fractions per week.

Surgery was scheduled 4 to 8 weeks after the last neoadjuvant treatment session, contingent upon the absence of surgical contraindications. Surgical options included McKeown or Ivor–Lewis esophagectomy performed via minimally invasive esophagectomy (MIE), right transthoracic open esophagectomy, or hybrid approaches combining video-assisted thoracoscopy with laparotomy. Standard practice involved performing two-field lymphadenectomy (Total two-field lymphadenectomy routine required), whereas three-field lymphadenectomy was reserved for patients presenting with clinically suspected lymph node enlargement in the cervical region. Patients with significant adhesion or intraoperative bleeding were converted to thoracotomy as needed.

Pathological analysis

Two experienced pathologists (YH Z and FL D) independently evaluated the pathology results, including tumor characteristics, depth of invasion, tumor regression grade (TRG), lymph node involvement, perineural invasion, angioinvasion, and resection margins. According to the 8th edition of the AJCC/UICC criteria for ypTNM staging [16], microscopic positivity (R1) was identified when a vital tumor was within 1 mm of any resection margin. A complete pathological response (pCR) indicated the absence of residual tumor. The TRG classifications were as follows: TRG 1a indicated no residual tumor, TRG 1b indicated < 10% residual tumor, TRG 2 indicated 10–50% residual tumor indicating partial regression, and TRG 3 indicated > 50% residual tumor, reflecting minimal or no treatment effect [17].

Follow-up

Patients were monitored postsurgery every 3 months in the first year and biannually in the second year for recovery and early detection of recurrence. Recurrence was categorized as locoregional (in areas such as remnant esophagus, stomach conduit, the supraclavicular, mediastinal, left gastric, or celiac trunk) or distant (confirmed via CT, MRI, or biopsy) metastasis. Disease-free survival (DFS) was defined as the period from surgery to recurrence or last follow-up/death, while overall survival (OS) spanned from neoadjuvant therapy onset to any-cause death or the final follow-up.The National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0, was used to evaluate the complications caused by neoadjuvant treatments [18]. Finally, the Clavien–Dindo classification was applied to assess the postoperative complication grades [19].

Statistical analysis

Statistical assessments were performed with R (v4.0.4). The chi-square test, Student's t test, Fisher's exact test and Mann–Whitney U test were used to compare baseline characteristics between the two groups. Propensity score matching (PSM) was performed with a 1:2 ratio and a 0.05 caliper to adjust for bias, which were significantly different between the groups. Variables impacting OS and DFS, identified through univariate analysis and with $p < 0.25$, were incorporated into Clustered Robust Cox Regression, strongly correlated factors (Spearman rank correlation coefficient > 0.7) with pathological stages were excluded from the multivariate Cox regression analysis. Despite its univariable insignificance, preoperative therapy was analyzed due to its primary study hypothesis. Survival outcomes were compared using Kaplan–Meier and log-rank tests, and $p < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

In this retrospective study, a total of 489 patients met the inclusion and exclusion criteria, comprising 161 patients who received nICT and 328 patients who were treated with nCRT (Fig. 1). Initial analysis of clinical characteristics revealed no significant differences between the two groups, with the exception of marked disparities in Eastern Cooperative Oncology Group (ECOG) performance status, smoking history, tumor location, clinical T stage, clinical N stage, clinical stage and the number of chemotherapy cycles (Table 1). To address potential biases stemming from these characteristics, 1:2 propensity score matching (PSM) was utilized, accounting for these variables. This resulted in a matched cohort consisting of 144 patients in the nICT group and 216 patients in the nCRT group. (Table 1).

Surgical and pathological outcomes

The nICT group demonstrated notable advantages in terms of lymph node dissection compared to the nCRT group (Table 2). Conversely, the nCRT group had superior pathological outcomes (Table 3). The pathological complete response (pCR) rate was significantly greater in the nCRT group (32.87% vs. 14.58% in the nICT group; $p < 0.001$). The nCRT group also had a better TRG, with 41.67% achieving TRG 1a, compared to 17.36% in the nICT group ($p < 0.001$). A lower incidence of perineural invasion (14.81% vs. 29.17%; $p = 0.002$) and angioinvasion

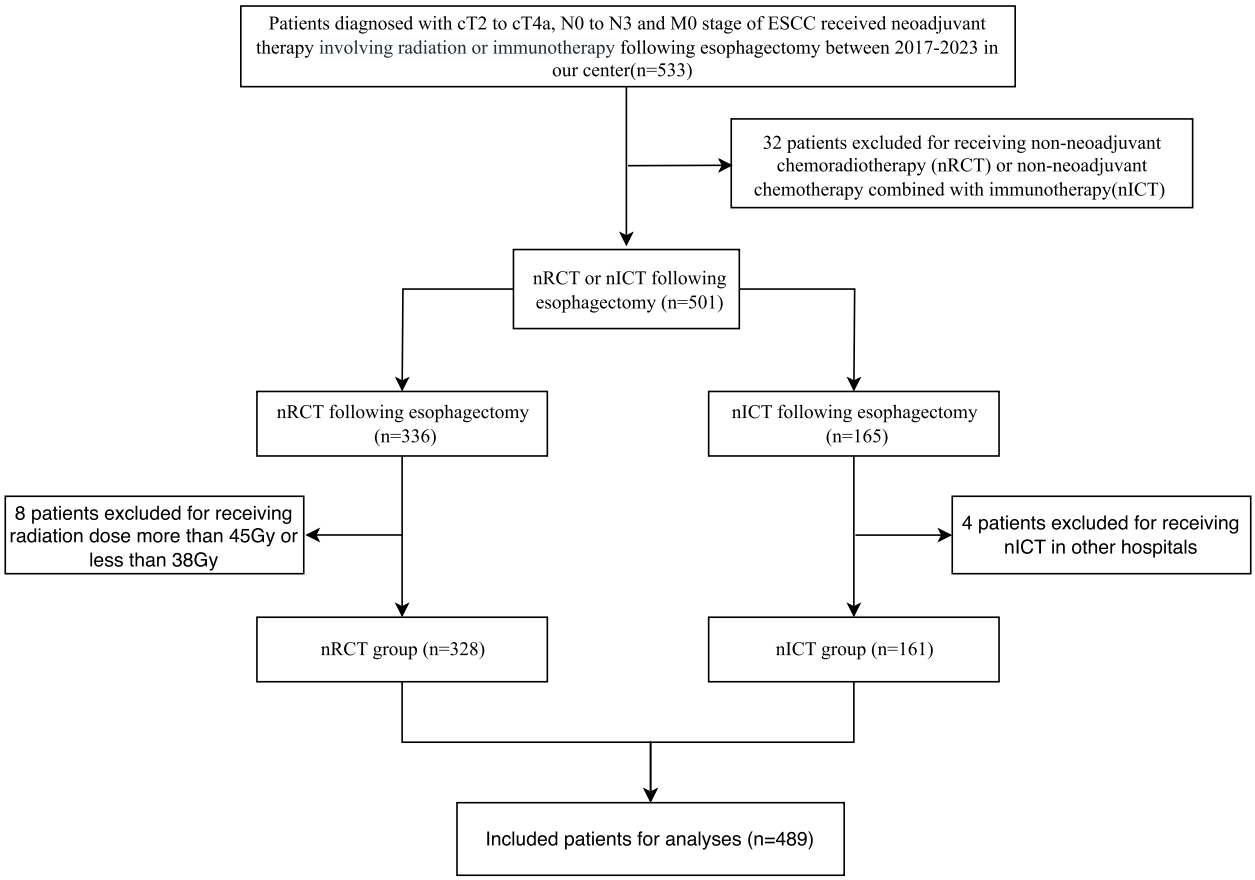

Fig. 1 CONSORT diagram of patient selection. ESCC, esophageal squamous cell carcinoma; nCRT, neoadjuvant chemoradiotherapy; nICT, neoadjuvant immunochemotherapy

(11.11% vs. 29.17%; $p < 0.001$) was observed in the nCRT group. However, there were no differences in ypN stage between the groups ($p = 0.108$).

Survival

The median follow-up duration for the entire study cohort was 27.7 months, ranging from 3.37 to 73 months. Initial analyses revealed no significant differences in DFS or OS between the nCRT and nICT groups (Fig. 2A/B). This similarity was further validated in matched samples. More precisely, the 3-year DFS rates were 58.32% (95% CI: 51.8–65.67) in the nCRT group and 56.16% (95% CI: 45.14–69.88) in the nICT group ($p = 0.670$ [Fig. 2C]). The 3-year OS rates were 69.96% (95% CI: 63.53–77.05) for the nCRT group and 71.99% (95% CI: 60.24–86.02) for the nICT group ($p = 0.990$ [Fig. 2D]).

Adverse effects and postoperative complications

Adverse events during neoadjuvant treatment are illustrated in Table 4. The results revealed that the nICT group had a lower incidence of grade 1 and 2 adverse events in all categories, except vomiting (31 of 144 [22.00%] vs 9 of 216 [4.20%]; $P < 0.001$). With respect to the risk of grade 3 and 4 adverse events, the nICT group also showed a lower incidence in terms of Radiation Esophagitis (0 of 144 [0%] vs 8 of 216 [3.70%]; $P = 0.024$), leukopenia (4 of 144 [2.80%] vs 63 of 216 [29.00%]; $P < 0.001$), and neutropenia (4 of 144 [2.80%] vs 52 of 216 [24.00%]; $P < 0.001$). The postoperative complication rates were not significantly different between the groups, except for a higher incidence of grade I and II liver function damage (29 of 144 [20.00%], 17 of 216 [7.90%]; $P < 0.001$) according to the Clavien-Dindo classification (Table 5). One patient in the nCRT group died because of severe systemic inflammation caused by an anastomotic leak.

Predictors of survival and recurrence patterns

Cox regression analysis was conducted on the matched samples to identify factors influencing survival. We eliminated TRG and pCR from the multivariate analysis because they had a strong correlation (Spearman rank correlation coefficient > 0.7) with the ypT stage. The multivariate Cox survival analysis revealed that R1/R2 resection, ypN1, and ypN2-3 were independent

Table 1 Clinicopathologic Characteristics of the Study Population before and after PSM

	Before PSM					After PSM				
	overall	nICT	nCRT	*P* value	SMD	overall	nICT	nCRT	*P* value	SMD
No.(%)	(*n*=489)	*n*=161	*n*=328			(*n*=360)	*n*=144	*n*=216		
Sex				0.340	0.107				0.421	0.104
Female	73 (14.9)	20 (12.4)	53 (16.2)			38 (10.6)	18 (12.5)	20 (9.3)		
Male	416 (85.1)	141 (87.6)	275 (83.8)			322 (89.4)	126 (87.5)	196 (90.7)		
Age				1.000	0.002				1.000	0.009
<60y	219 (44.8)	72 (44.7)	147 (44.8)			161 (44.7)	64 (44.4)	97 (44.9)		
≥60y	270 (55.2)	89 (55.3)	181 (55.2)			199 (55.3)	80 (55.6)	119 (55.1)		
BMI				0.274	0.117				0.311	0.122
<24	341 (69.7)	118 (73.3)	223 (68.0)			253 (70.3)	106 (73.6)	147 (68.1)		
≥24	148 (30.3)	43 (26.7)	105 (32.0)			107 (29.7)	38 (26.4)	69 (31.9)		
ECOG				<0.001	0.440				0.803	0.044
0	428 (87.5)	155 (96.3)	273 (83.2)			343 (95.3)	138 (95.8)	205 (94.9)		
1	61 (12.5)	6 (3.7)	55 (16.8)			17 (4.7)	6 (4.2)	11 (5.1)		
Smoking				0.017	0.239				0.394	0.095
No	154 (31.5)	39 (24.2)	115 (35.1)			94 (26.1)	34 (23.6)	60 (27.8)		
Yes	335 (68.5)	122 (75.8)	213 (64.9)			266 (73.9)	110 (76.4)	156 (72.2)		
Drinking				0.565	0.065				0.871	0.030
No	165 (33.7)	51 (31.7)	114 (34.8)			112 (31.1)	46 (31.9)	66 (30.6)		
Yes	324 (66.3)	110 (68.3)	214 (65.2)			248 (68.9)	98 (68.1)	150 (69.4)		
Tumor Location				<0.001	0.480				0.104	0.265
Upper third	7 (1.4)	2 (1.2)	5 (1.5)			6 (1.7)	2 (1.4)	4 (1.9)		
Middle third	197 (40.3)	89 (55.3)	108 (32.9)			162 (45.0)	76 (52.8)	86 (39.8)		
Lower third	208 (42.5)	55 (34.2)	153 (46.6)			154 (42.8)	52 (36.1)	102 (47.2)		
Gastroesoph-ageal junction	77 (15.7)	15 (9.3)	62 (18.9)			38 (10.6)	14 (9.7)	24 (11.1)		
Clinical T stage				<0.001	0.537				0.716	0.090
T2	19 (3.9)	3 (1.9)	16 (4.9)			7 (1.9)	3 (2.1)	4 (1.9)		
T3	393 (80.4)	150 (93.2)	243 (74.1)			331 (91.9)	134 (93.1)	197 (91.2)		
T4a	77 (15.7)	8 (5.0)	69 (21.0)			22 (6.1)	7 (4.9)	15 (6.9)		
Clinical N stage				0.005	0.316				0.929	0.072
N0	21 (4.3)	14 (8.7)	7 (2.1)			9 (2.5)	4 (2.8)	5 (2.3)		
N1	156 (31.9)	45 (28.0)	111 (33.8)			115 (31.9)	45 (31.2)	70 (32.4)		
N2	256 (52.4)	81 (50.3)	175 (53.4)			193 (53.6)	76 (52.8)	117 (54.2)		
N3	56 (11.5)	21 (13.0)	35 (10.7)			43 (11.9)	19 (13.2)	24 (11.1)		

Table 1 (continued)

No.(%)	Before PSM overall (*n*=489)	nICT *n*=161	nCRT *n*=328	*P* value	SMD	After PSM overall (*n*=360)	nICT *n*=144	nCRT *n*=216	*P* value	SMD
Clinical Stage				0.008	0.299				0.913	0.045
II	27 (5.5)	14 (8.7)	13 (4.0)			11 (3.1)	5 (3.5)	6 (2.8)		
III	343 (70.1)	119 (73.9)	224 (68.3)			288 (80.0)	114 (79.2)	174 (80.6)		
IVA	119 (24.3)	28 (17.4)	91 (27.7)			61 (16.9)	25 (17.4)	36 (16.7)		
Chemotherapy cycles				0.025	0.264				1.000	0.024
1 cycle	45 (9.2)	9 (5.6)	36 (11.0)			21 (5.8)	8 (5.6)	13 (6.0)		
2 cycles	419 (85.7)	139 (86.3)	280 (85.4)			326 (90.6)	131 (91.0)	195 (90.3)		
3-4 cycles	25 (5.1)	13 (8.1)	12 (3.7)			13 (3.6)	5 (3.5)	8 (3.7)		

Note: *PSM* Propensity score matching, *SMD,* Standardised mean difference, *nICT* neoadjuvant chemotherapy and immunotherapy, *nCRT* neoadjuvant chemoradiotherapy, *BMI* Body mass index, *MIN* Minimum, *MAX* Maximum, *ECOG* Eastern Cooperative Oncology performance status

Table 2 Surgical Characteristics of Patients after PSM

No.(%)	nICT 144	nCRT 216	*P* value
Procedure type			0.059
McKeown	126 (87.50)	202 (93.52)	
Ivor-lewis	18 (12.50)	14 (6.48)	
Cervical LN dissection			<0.001
No	79 (55.63)	197 (91.20)	
Yes	63 (44.37)	19 (8.80)	
No. of dissected LN stations (median [IQR])			0.004
	9.00 [7.00, 12.00]	9.00 [7.000, 10.00]	
No. of removed LN (median [IQR])			<0.001
	26.00 [19.00, 34.00]	17.00 [12.00, 23.00]	
Resection			1.000
R0	135 (93.75)	202 (93.52)	
R1/R2	9 (6.25)	14 (6.48)	

Note: *PSM* Propensity Score Matching, *nICT* neoadjuvant chemotherapy and immunotherapy, *nCRT* neoadjuvant chemoradiotherapy, *LN* lymph node

factors associated with poorer DFS (hazard ratio [HR] for R1/R2 resection = 2.256, 95% confidence interval [CI]:1.407–3.616, $p < 0.001$; HR for ypN1 = 1.916, 95% CI: 1.157–3.173; and HR for ypN2-3 = 3.299, 95% CI:1.855–5.869, $p < 0.001$; Supplementary Table 1). Additionally, ECOG 1 (HR = 1.693, 95% CI:1.179–2.431, $p = 0.004$) and ypN2-3 (HR = 3.055, 95% CI:1.521–6.133, $p = 0.006$) were independently associated with poorer OS (Supplementary Table 2). The LRR incidence in the nICT group was higher than in the nCRT group, although the difference was not statistically significant (3-year LRR rates: 36.58% vs 23.58%, $p = 0.065$, Fig. 3A). The rates of distant metastasis (DM) were similar between the nICT and nCRT groups (3-year DM rates: 31.95% vs 26.57%, $p = 0.390$, Fig. 3B).

Discussion

This retrospective study of neoadjuvant therapy in patients with ESCC showed that patients who underwent nICT followed by surgery had poorer pathologic outcomes in terms of pCR rates, tumor regression grade, perineural invasion, and angioinvasion rates than those who underwent nCRT. However, the initial survival analysis revealed similar overall and disease-free survival among patients who received nICT followed by surgery compared with those treated with nCRT followed by surgery. These results imply a complicated and possibly multifaceted link between the type of neoadjuvant therapy, pathologic outcomes, and final survival.

Since the FDA's 2012 endorsement of pCR as a surrogate endpoint for neoadjuvant studies, its use has increased, underpinned by the notion that higher pCR rates may predict clinical benefit [20]. Studies, including Kamarajah et al.'s analysis and the NEOCRTEC5010 trial, have confirmed that pCR is associated with improved overall survival in patients with esophageal squamous cell carcinoma, highlighting its significance as a prognostic indicator [21, 22]. Consequently, research on neoadjuvant therapy focuses more on reaching a higher rate of pathological complete response (pCR) once surgical safety has been demonstrated. Recent studies have highlighted the safety of neoadjuvant immunochemotherapy (nICT) in treating locally advanced esophageal squamous cell carcinoma (ESCC), with some reports suggesting a better safety profile than neoadjuvant chemoradiotherapy (nCRT) [11, 12].

The comparison of nCRT and nICT outcomes for esophageal squamous cell carcinoma (ESCC) yields varied results. While Cheng et al. [12] reported similar pCR rates between the nCRT and nICT groups, with nICT reaching up to 37.5% pCR, another phase II study showed that nIC [10], specifically camrelizumab combined with chemotherapy, achieved a 39.2% pCR rate. However, Hong et al. [11] reported that the pCR rate of patients treated with nICT was significantly lower than that of patients treated with nCRT (18.8% vs 43.8%; $P = 0.003$), a finding consistent with our findings that favored nCRT. However, comparisons across studies require caution due to variations in treatment protocols, tumor mutational burden (TMB) and treatment sequencing. For instance, sequencing chemotherapy with anti-PD-1 therapy and the number of neoadjuvant cycles have been shown to impact nICT efficacy [23]. Another study revealed that the number of neoadjuvant cycles (HR: 5.271, 95% CI: 1.278—21.740, $p = 0.022$) was an independent predictor of good tumor and nodal response [24]. Conversely, no

Table 3 Pathologic Outcomes of Patients after PSM

No.(%)	nICT *N*=144	nCRT *N*=216	*P* value
pCR			<0.001
No	123 (85.42)	145 (67.13)	
Yes	21 (14.58)	71 (32.87)	
TRG			<0.001
1a	25 (17.36)	90 (41.67)	
1b	13 (9.03)	42 (19.44)	
2	47 (32.64)	72 (33.33)	
3	59 (40.97)	12 (5.56)	
Perineural invasion			0.002
No	102 (70.83)	184 (85.19)	
Yes	42 (29.17)	32 (14.81)	
Angioinvasion			<0.001
No	102 (70.83)	192 (88.89)	
Yes	42 (29.17)	24 (11.11)	
ypT stage			<0.001
ypT0	25 (17.36)	90 (41.67)	
ypT1	26 (18.06)	27 (12.50)	
ypT2	31 (21.53)	45 (20.83)	
ypT3-4a	62 (43.06)	54 (25.00)	
ypN stage			0.108
N0	83 (57.64)	139 (64.35)	
N1	31 (21.53)	50 (23.15)	
N2-3	30 (20.83)	27 (12.50)	

Note: *PSM* Propensity score matching, *nCRT* neoadjuvant chemoradiotherapy, *nICT* neoadjuvant chemotherapy and immunotherapy, *TRG* Tumor regression grade, *pCR* pathological complete regression

statistically significant association was observed between PD-L1 status and pathological response in esophageal squamous cell carcinoma (ESCC), irrespective of the method used to assess PD-L1 expression [10]. Factors such as late clinical stage, fewer neoadjuvant cycles, and concurrent chemotherapy and immunotherapy may explain the lower pathological outcomes in our study. Furthermore, lower TRG scores, perineural invasion and angioinvasion postneoadjuvant therapy are linked to prognosis [25–29], with our study indicating the superiority of nCRT in these aspects as well as pCR rates.

In fact, the notion that a better pathological response does not lead to improved survival rates may seem counterintuitive. Notably, compared to those in the nCRT group, a greater number of patients in the nICT group underwent supraclavicular lymph node dissection, involving more lymph node stations and a greater quantity of nodes removed. However, further analysis revealed that among the various factors affecting survival, only the pathological stage of the postoperative lymph nodes served as an independent prognostic factor. The nCRT group generally had better pathological outcomes than did the nICT group, yet no significant differences in postsurgical lymph node stage were observed. Samson et al. [30] indicated that neoadjuvant therapy type does not independently predict survival ($p=0.12$), despite higher pCR rates with chemoradiation (17.2% versus 6.4%, $p<0.001$). Similarly, Spicer et al. [31] reported that the number of positive lymph nodes postsurgery is a significant survival determinant. Further investigation of the impact of pathological response status on long-term survival in the NEOCRTEC5010 trial demonstrated that the ypTanyN0M0 group exhibited better survival than both the ypT0NanyM0 and ypTanyNanyM0 groups [22], highlighting the paramount importance of lymph node pathology in survival outcomes. One explanation might be that comprehensive surgical excision was performed in both groups, ensuring that the removal of lesions did not achieve pCR. Additionally, the JCOG1109 NExT Study [32] revealed that cisplatin plus fluorouracil (CF) alone resulted in lower pCR rates than radiotherapy with CF (CF-RT) did (2.1% vs 38.5%), with no significant difference in OS rates (62.6% vs 68.3%, $p=0.12$). The increase in the number of noncancer deaths in the CF-RT group indicates that potential long-term risks may counteract the survival advantages of higher pCR rates. Our research also revealed a tendency for the ECOG score to affect patients' overall survival (OS). In addition, the Checkmate 577 trial [33] showed that nivolumab adjuvant therapy significantly improved disease-free survival in esophageal cancer patients who did not respond to neoadjuvant chemoradiotherapy, suggesting that the survival benefits of patients receiving adjuvant therapy might surpass those of patients who achieved a pathologic complete response. This may explain the lack of survival benefit in the nCRT group despite their significant pathological response.

Although propensity score matching (PSM) and strict patient selection were used to reduce bias, the retrospective design of this study still has limitations. Firstly, this was a single-center retrospective study, despite the inclusion of a large sample size. Secondly, a significant limitation is the exclusion of patients who did not respond to neoadjuvant therapy. Additionally, inconsistent chemotherapy and checkpoint blockade regimens, along with the failure to account for the effect of postoperative adjuvant therapy, may have distorted survival outcomes.

Conclusions

Our study showed that although nCRT was superior to nICT in terms of pathological response, this advantage did not translate into a survival benefit, with only a small and statistically insignificant advantage in local control over nICT. Additionally, nCRT has a relatively high incidence of toxic side effects during neoadjuvant therapy,

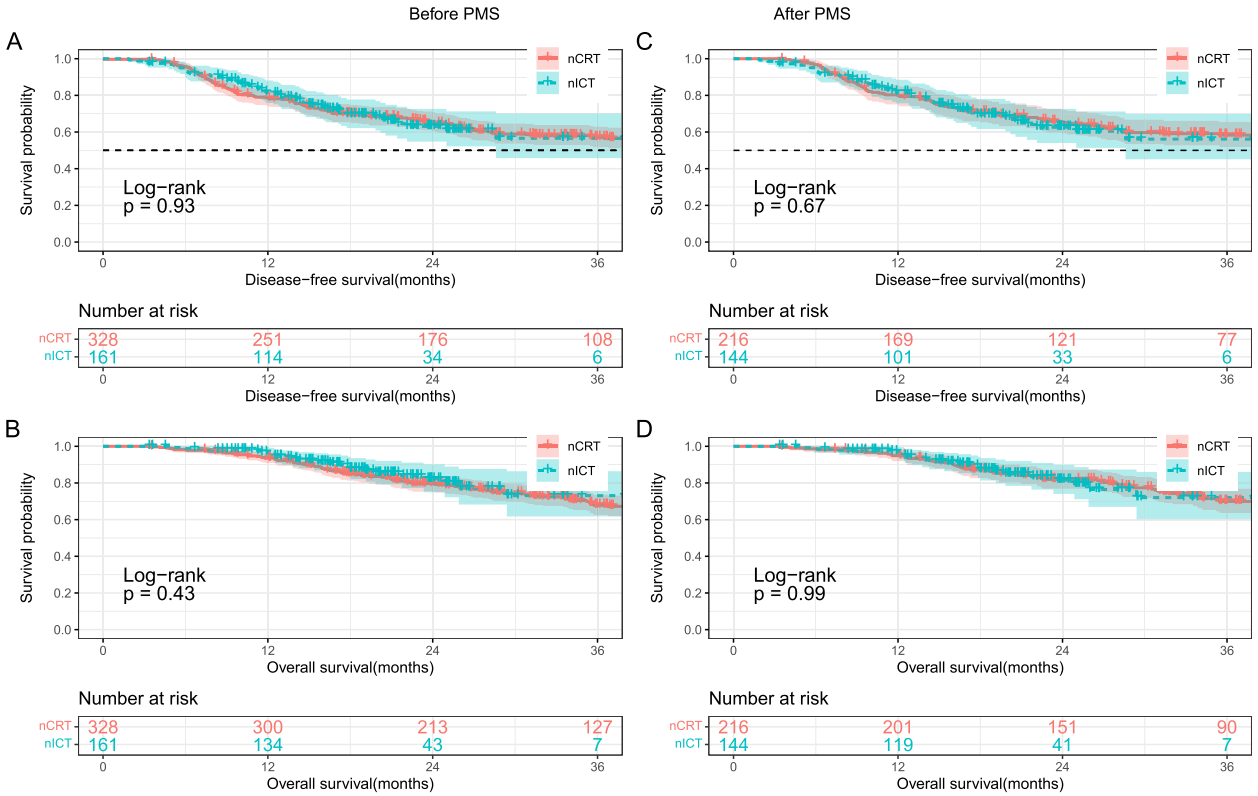

Fig. 2 Disease-free survival (DFS) (**A**) and overall survival (OS) (**B**) in the 2 treatment groups before propensity score matching (PSM) and DFS (**C**) and OS (**D**) in the matched samples. nCRT, neoadjuvant chemoradiotherapy; nICT, neoadjuvant immunochemotherapy

Table 4 Adverse Events During Neoadjuvant Treatment after PSM

	nICT	nCRT	*P* value
Grade 1 and 2, No.(%)	144	216	
Vomiting	31 (22%)	9 (4.2%)	<0.001
Anorexia	10 (6.9%)	51 (24%)	<0.001
Fatigue	4 (2.8%)	1 (0.5%)	0.086
Diarrhea	4 (2.8%)	7 (3.2%)	>0.999
Constipation	12 (8.3%)	56 (26%)	<0.001
Pulmonary Infection	0 (0%)	9 (4.2%)	0.013
Radiation Esophagitis	0 (0%)	134 (62%)	<0.001
Noninfectious Pneumonia	15 (10%)	60 (28%)	<0.001
Liver Dysfunction	7 (4.9%)	9 (4.2%)	0.754
Anemia	54 (38%)	92 (43%)	0.335
Thrombocytopenia	15 (10%)	58 (27%)	<0.001
Leukopenia	30 (21%)	121 (56%)	<0.001
Neutropenia	9 (6.3%)	68 (31%)	<0.001
Grade 3 and 4, No.(%)	144	216	
Vomiting	0 (0%)	7 (3.2%)	0.045
Pulmonary Infection	1 (0.7%)	1 (0.5%)	>0.999
Radiation Esophagitis	0 (0%)	8 (3.7%)	0.024
Leukopenia	4 (2.8%)	63 (29%)	<0.001
Neutropenia	4 (2.8%)	52 (24%)	<0.001

Note: *PSM* Propensity score matching, *nICT* neoadjuvant immunochemotherapy, *nCRT* neoadjuvant chemoradiotherapy

Table 5 Postoperative Morbidity and Mortality after PSM

	nICT	nCRT	*P* value
Clavien-Dindo grade I and II, No.(%)	144	216	
Pulmonary Infection	21 (15%)	33 (15%)	0.857
Liver Function Damage	29 (20%)	17 (7.9%)	<0.001
Pneumothorax	2 (1.4%)	0 (0%)	0.159
Intrathoracic Abscess	2 (1.4%)	0 (0%)	0.159
Arrhythmia	14 (9.7%)	19 (8.8%)	0.765
Anastomotic Leakage	12 (8.3%)	10 (4.6%)	0.151
Chylothorax	3 (2.1%)	0 (0%)	0.063
Recurrent Nerve Injury	3 (2.1%)	2 (0.9%)	0.393
Wound Infection	4 (2.8%)	8 (3.7%)	0.769
Pleural Effusion	31 (22%)	26 (12%)	0.016
Clavien-Dindo grade III-V, No.(%)	144	216	
Pulmonary Infection	26 (18%)	22 (10%)	0.031
Pneumothorax	7 (4.9%)	9 (4.2%)	0.754
Anastomotic Leakage	13 (9.0%)	14 (6.5%)	0.369
Chylothorax	0 (0%)	5 (2.3%)	0.162
Wound Infection	1 (0.7%)	1 (0.5%)	>0.999
Pleural Effusion	21 (15%)	39 (18%)	0.386

Note: *PSM* Propensity score matching, *nICT* neoadjuvant immunochemotherapy, *nCRT* neoadjuvant chemoradiotherapy

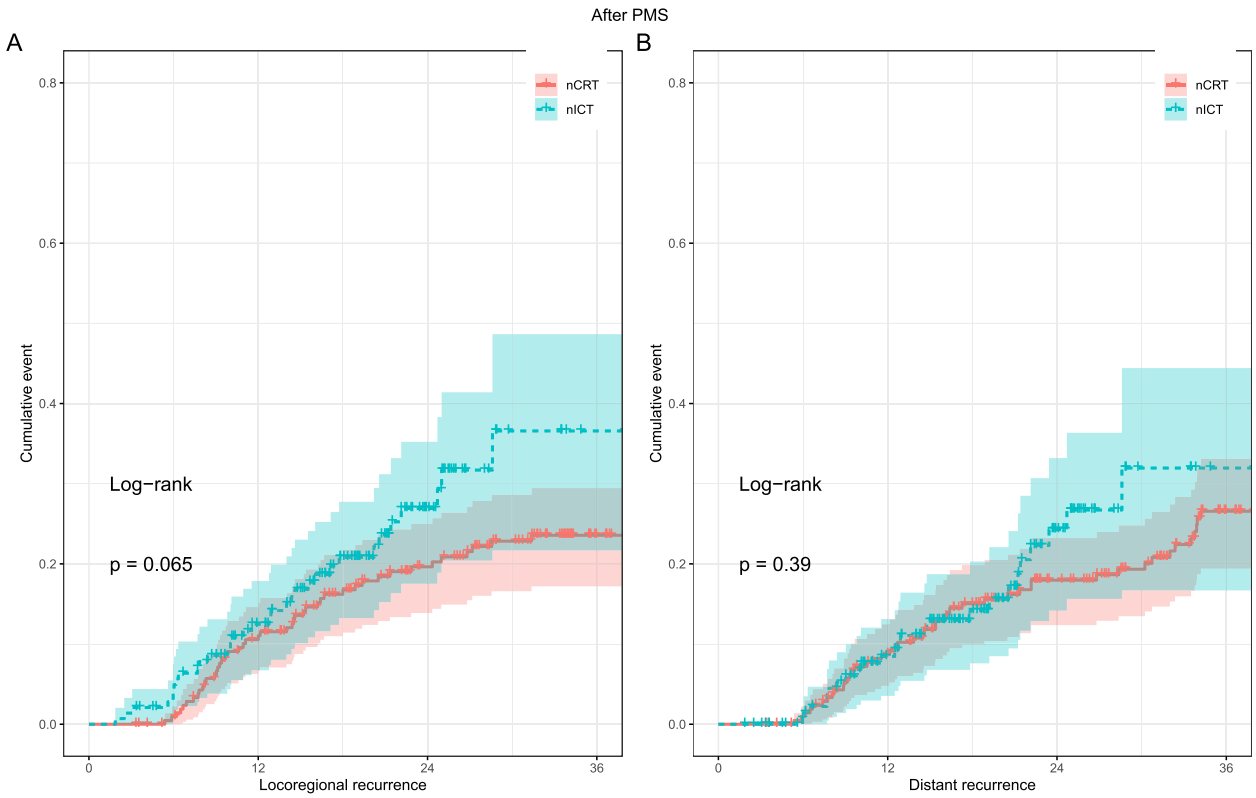

Fig. 3 Locoregional recurrence (LRR) (**A**) and distant metastasis (**B**) in the matched samples. nCRT, neoadjuvant chemoradiotherapy; nICT, neoadjuvant immunochemotherapy

but the incidence of postoperative complications is similar between the two treatments. These results underscore the importance of improving prognosis prediction technology to more accurately choose treatment interventions. Further phase III clinical trials are needed to clarify the roles of nICT and nCRT in the treatment of locally advanced esophageal squamous cell carcinoma (ESCC), and more definitive evidence is required to guide treatment selection.

Abbreviations

nCRT	Neoadjuvant chemoradiotherapy
nICT	Neoadjuvant immunotherapy
ESCC	Esophageal squamous cell carcinoma
PSM	Propensity score matching
TRG	Tumor regression grade
pCR	Complete pathological response
DFS	Disease-free survival
OS	Overall survival
ECOG	Eastern Cooperative Oncology Group
MIE	Minimally invasive esophagectomy
LRR	Locoregional recurrence

Supplementary Information

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Supplementary Materials 1.

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Authors' contributions
Study concept and design: QW, XZ. Data collection and quality control: LL, YZ, LP. Data analysis and construction of tables and figures: HH, LW. Manuscript draft and results interpretation: YW, HZ, KM. Critical revision of the manuscript for important intellectual content: all authors. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Sichuan Cancer Hospital & Institute, Sichuan Cancer Center (ethical approval number SCCHEC-02–2023-029). Informed consent was waived by the ethics committee.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Radiation Oncology Key Laboratory of Sichuan Province, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, No.55, Section 4, South Renmin Road, Chengdu 610042, China. [2]Department of Thoracic Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, No. 55, Section 4, South Renmin Road, Chengdu 610042, China. [3]School of Medicine, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China. [4]Department of Pathology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, China.

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