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ORIGINAL RESEARCH

Optimal Treatment Strategies for Resectable Locally Advanced Esophageal Squamous Cell Carcinoma: A Real-World Triple Cohort Analysis Using Propensity Score Matching

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Purpose: This study aims to identify the most effective treatment approach and compares the survival rates, along with complications, in patients with locally resectable esophageal squamous cell carcinoma (ESCC) who were treated with one of the three treatment patterns: neoadjuvant chemotherapy followed by surgery (NCT+S), neoadjuvant chemoradiotherapy followed by surgery (NCRT+S), or surgery followed by chemoradiotherapy (S+CRT).

Methods: We conducted a retrospective analysis of the medical records of ESCC patients who received one of these treatments between March 2015 and March 2022. This analysis aimed to identify differences in long-term survival, pathological responses, and complications across the three treatment groups. To address potential confounding factors, propensity score matching (PSM) and Cox proportional hazards models were utilized.

Results: This study included a cohort of 715 patients: 197 in the NCT+S group, 188 in the NCRT+S group, and 330 in the S+CRT group, all meeting the selection criteria. After PSM, the median disease-free survival (DFS) time was 38.9 months, 25.6 months, and 15.3 months for NCRT+S, NCT+S, and S+CRT groups, respectively. There were statistically significant differences in the 5-year DFS and 5-year OS among the three groups (P=0.04 and P=0.02, post-matching, respectively). Notably, neoadjuvant therapy showed a correlation with increased postoperative anastomotic leakage rates (17.5% in NCRT+S, 10% in NCT+S, and 5% in S+CRT; P=0.03, post-matching), regardless of the PSM adjustment.

Conclusion: The findings indicate that neoadjuvant therapy before surgery offers a significant survival advantage over postoperative adjuvant therapy for patients with locally advanced resectable ESCC. Despite similar safety profiles, neoadjuvant therapy appears to be associated with a higher incidence of anastomotic leakage after surgery.

Keywords: neoadjuvant therapy, esophageal squamous cell carcinoma, postoperative adjuvant therapy, prognosis

Introduction

In 2020, esophageal cancer (EC) was the seventh most commonly diagnosed cancer worldwide, with approximately 604,000 new cases, and it ranked sixth in mortality, resulting in about 544,000 deaths.[1] A study utilizing cancer registry data revealed that esophageal squamous cell carcinoma (ESCC) is the main histological subtype in China, accounting for 85.79% of the cases reported.[2] Coordinated multidisciplinary treatment approaches are crucial for effectively managing locally advanced EC. Numerous key clinical studies[3–6] have supported the use of neoadjuvant therapy, encompassing

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neoadjuvant chemoradiotherapy (NCRT) or neoadjuvant chemotherapy (NCT) followed by surgical intervention, as the preferred treatment for resectable EC. The CROSS[3] and NEOCRTEC5010[4] trials were instrumental in establishing NCRT as the standard approach for treating locally advanced operable ESCC, demonstrating superior overall survival (OS) compared to surgery alone. Studies such as OEO2[5] and MAGIC[6] indicated that NCT succeeded by surgery could improve 5-year OS by 6% and 13%, respectively, when compared to surgery alone. The National Comprehensive Cancer Network does not recommend postoperative adjuvant therapy for EC,[7] whereas Chinese ESCC guidelines advise postoperative chemotherapy, radiotherapy, or chemoradiotherapy for patients with pN+ and pT3-4a ESCC to improve prognosis.[8]

Two prospective studies have investigated the efficacy of NCRT and NCT in the treatment of locally advanced ESCC. The JCOG1109NExT three-arm Phase III trial demonstrated that the combination of docetaxel, cisplatin, and 5-FU (DCF) significantly enhanced OS when compared to the cisplatin and 5-FU (CF) dual-therapy regimen. Additionally, the study observed no significant difference in 3-year OS rates between the dual-agent chemotherapy and NCRT cohorts.[9] A prospective multicenter randomized trial in China (CMISG1701) also indicated equivalent OS and progression-free survival between locally advanced ESCC patients treated with NCRT and NCT.[10] Nevertheless, several studies suggest that postoperative adjuvant chemotherapy or radiotherapy can substantially reduce local recurrence and enhance patient survival in comparison to surgery alone.[11,12] Only a few studies have examined the effects of varying the sequence of surgical and chemoradiotherapy on the prognosis of patients with resectable ESCC.

In response to this gap, we executed a real-world propensity score-matched (PSM) study, aiming to identify the most efficacious treatment approach and assess the differences in survival, as well as complications among resectable ESCC patients who underwent NCT followed by surgery (NCT+S), NCRT followed by surgery (NCRT+S), or surgery followed by chemoradiotherapy (S+CRT).

Patients and Methods

Patients Selection

We conducted a retrospective analysis of ESCC patients who underwent NCRT, NCT plus esophagectomy, or esophagectomy plus adjuvant CRT at our institution between March 2015 and March 2022. The inclusion criteria for this study: histopathological confirmation of ESCC; locally advanced disease stage appropriate for surgical resection (cT1-2N+ and cT3-4aN0/N+), as per the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) Classification; Eastern Cooperative Oncology Group performance status of 0–1; normal hematologic, hepatic, and renal functions, and no history of other malignancies. The research protocol was approved by the Ethics Committee of Cancer Hospital Affiliated to Shandong First Medical University. As this was a retrospective investigation, the necessity for written informed consent was exempted.

Chemotherapy

Both preoperative and postoperative concurrent chemotherapy primarily included platinum-based and fluorouracil drugs (PF regimen), or platinum-based drugs combined with docetaxel, paclitaxel, or albumin paclitaxel (taxane-platinum regimen), all administered intravenously. The PF regimen consisted of platinum-based drugs (nedaplatin at 75 mg/m2, carboplatin with an area under the curve of 5, or cisplatin at 25 mg/m2 on days 1–3) and fluorouracil at 50 mg/m2 on days 1–5 or alternatively S-1 at 60 mg/m2/day orally twice a day on days 1–14. In contrast, the taxane-platinum regimen contained docetaxel (75 mg/m2), paclitaxel (135–175 mg/m2), or albumin-bound paclitaxel (260 mg/m2). Patients in the NCT and NCRT groups typically received 1–3 cycles of preoperative chemotherapy (either PF or taxane-platinum regimens) every three weeks, with an average of two cycles. For the S+CRT group, patients were administered 2–6 cycles of postoperative adjuvant chemotherapy (either PF or taxane-platinum regimens) every three weeks, with a median of four cycles.

Radiotherapy

Patients in the NCRT group were subjected to radiation doses ranging from 40 to 50.4 Gy, while those in the S+CRT group received radiation doses from 45 to 50.4 Gy. Both sets of patients were administered these doses in fractions of 1.8–2.0 Gy, following a schedule of five fractions per week. The radiotherapy techniques employed were intensity-modulated radiation therapy or volumetric intensity-modulated arc therapy, both using 6 MV X-rays.

Surgical Treatment

Several esophagectomy techniques were performed, including thoracostomy esophagectomy or minimally invasive esophagectomy (MIE), each paired with gastric reconstruction and standard lymphadenectomy. The two primary radical surgeries for ESCC mainly include the left thoracic approach esophagectomy (Sweet procedure) and the right thoracic, upper abdominal, and left neck three-incision esophagectomy (McKeown procedure). Esophagectomies were scheduled 4–6 weeks after neoadjuvant therapy in both the NCT and NCRT groups.

Pathology

The pathological TNM stage diagnoses were independently assessed by two pathologists utilizing hematoxylin and eosin staining alongside immunohistochemistry. Their assessments conformed to the protocols outlined in the 8th edition of the AJCC guidelines. The tumor regression grade (TRG) was categorized into four grades, from 0 to 3, based on the criteria by the College of American Pathologists.[7] Complete pathologic response (pCR) was defined as an absence of viable tumor cells (grade 0); otherwise, cases were designated as having a non-complete pathologic response (non-pCR) (grade 1 consisted of residual solitary tumor cells or small clusters of tumor cells; grade 2 referred to partial tumor residuals with substantial interstitial fibrosis; and grade 3 indicated negligible or absent tumor cell regression). An R0 resection, indicating a complete tumor resection with a negative microscopic incision margin signifying no residual tumor, was the target outcome.

Follow-Up

The initial follow-up was scheduled one month post-surgery. Thereafter, patients were followed up every three months in the initial two years, bi-annually from the third to the fifth year, and annually until the conclusion of the study. Each follow-up encompassed a medical history review, physical examination, hematological testing, and a comprehensive imaging suite which included cervical, chest, and abdominal computed tomography (CT), along with upper gastrointestinal radiography. If deemed necessary, additional assessments like gastroscopy, magnetic resonance imaging, positron emission tomography-CT, and bone scans were conducted.

Statistical Analysis

Disease-free survival (DFS) was defined as the interval from surgery to the time of disease progression or the last follow-up. OS was determined as the period from the first day of treatment until death or the last follow-up.

For quantitative data, when the distribution is normal, a *t*-test is used for comparisons between two groups, and analysis of variance is employed for three or more groups. If the distribution is not normal, the Mann–Whitney *U*-test is used for two groups, and the Kruskal–Wallis test is applied for three or more groups. For categorical data, Fisher's exact test or chi-square tests are employed. DFS and OS across the three groups were compared employing the Kaplan–Meier method and the Log rank test. A Cox proportional hazards model was used to adjust for confounding factors and to identify independent predictors of OS and DFS, with significance set at $P < 0.05$.

In order to reduce the effects of confounding factors on outcomes across the groups, we applied a 1:1 PSM technique using the nearest neighbor algorithm (caliper: 0.2). The propensity score was determined using a logistic regression model based on the following confounding variables: sex, age (categorized as ≥60 years or not), smoking history, alcohol use history, comorbidities, family history of malignancy, tumor location, and clinical T and N stages (classified as T1, T2, T3, T4, and N0 or N+). All statistical analyses were performed using SPSS 24.0 for Windows (IBM Corp, Chicago, IL) and R version 4.2.1.

Results

Patient Characteristics

A total of 715 patients meeting the inclusion criteria were included in the study, distributed as follows: 197 underwent NCRT, 188 had NCT, and 330 received surgery followed by CRT. There were significant differences in age (P=0.033), tumor location (P=0.002), and clinical stage (P<0.001) among the three unbalanced groups. To minimize confounding bias, we implemented a 1:1 PSM study involving the NCRT (n = 80), NCT (n = 80), and S+CRT (n = 80) cohorts. Post-PSM, clinical characteristics were well distributed across the three groups. We did not include chemotherapy regimens as a factor for propensity score matching because, before PSM, 12.7% of patients in the S+CRT group only received adjuvant radiotherapy post-surgery, most of whom were at clinical stage T3N0. This also resulted in variations in chemotherapy regimens among the groups. The baseline clinical characteristics of the three groups, both before and after PSM, are detailed in Table 1.

Surgery-Related Procedures

Significant differences were found among the three groups, before and after PSM, regarding the surgical approach, surgical type, and lymph node dissection counts (as shown in Table 2). The distribution of open esophagectomy (OE) and MIE significantly varied among the groups, with a higher prevalence of OE in the NCT and S+CRT groups compared to the NCRT group (73.8% vs 75% vs 51.2%, respectively; P=0.011 post-PSM). After PSM, within the NCRT group, three patients (3.8%), two patients (2.5%) in the NCT group, and one patient (1.2%) in the S+CRT group initially intended for

Table 1 Comparison of Baseline Clinical Characteristics Among Three Groups Before and After Propensity Score Matching

Clinical Characteristics	Before Matching				After Matching			
	NCT (n=188)	NCRT (n=197)	S+CRT (n=330)	*P* value	NCT (n=80)	NCRT (n=80)	S+CRT (n=80)	*P* value
Sex†								
Male	152 (80.9%)	173 (87.8%)	280 (84.8%)	0.164	66 (82.5%)	67 (83.8%)	71 (88.8%)	0.503
Female	36 (19.1%)	24 (12.2%)	50 (15.2%)		14 (17.5%)	13 (16.2%)	9 (11.2%)	
Age (year)†								
<60	75 (39.9%)	86 (43.7%)	108 (32.7%)	0.033	29 (36.2%)	33 (41.2%)	32 (40.0%)	0.797
≥60	113 (60.1%)	111 (56.3%)	222 (67.3%)		51 (63.7%)	47 (58.8%)	48 (60.0%)	
History of smoking†								
No	81 (43.1%)	79 (40.1%)	136 (41.2%)	0.835	33 (41.2%)	40 (50.0%)	29 (36.2%)	0.205
Yes	107 (56.9%)	118 (59.9%)	194 (58.8%)		47 (58.8%)	40 (50.0%)	51 (63.7%)	
History of alcohol†								
No	94 (50.0%)	82 (41.6%)	167 (50.6%)	0.110	35 (43.8%)	44 (55.0%)	40 (50.0%)	0.362
Yes	94 (50.0%)	115 (58.4%)	163 (49.4%)		45 (56.2%)	36 (45.0%)	40 (50.0%)	
Comorbidity†								
No	126 (67.0%)	128 (65.0%)	227 (68.8%)	0.663	51 (63.7%)	50 (62.5%)	54 (67.5%)	0.789
Yes	62 (33.0%)	69 (35.0%)	103 (31.2%)		29 (36.2%)	30 (37.5%)	26 (32.5%)	
ECOG†								
0	140 (74.5%)	149 (75.6%)	249 (75.5%)	0.959	57 (71.2%)	60 (75.0%)	60 (75.0%)	0.824
1	48 (25.5%)	48 (24.4%)	81 (24.5%)		23 (28.7%)	20 (25.0%)	20 (25.0%)	
Family history†								
No	174 (92.6%)	183 (92.9%)	303 (91.8%)	0.895	73 (91.2%)	72 (90.0%)	74 (92.5%)	0.855
Yes	14 (7.4%)	14 (7.1%)	27 (8.2%)		7 (8.8%)	8 (10.0%)	6 (7.5%)	
Tumor localization†								
Lower	67 (35.6%)	102 (51.8%)	130 (39.4%)	0.002	35 (43.8%)	37 (46.2%)	33 (41.2%)	0.353
Middle	96 (51.1%)	79 (40.1%)	177 (53.6%)		33 (41.2%)	34 (42.5%)	42 (52.5%)	
Upper	25 (13.3%)	16 (8.1%)	23 (7.0%)		12 (15.0%)	9 (11.2%)	5 (6.2%)	

(*Continued*)

Table 1 (Continued).

Clinical Characteristics	Before Matching				After Matching			
	NCT (n=188)	NCRT (n=197)	S+CRT (n=330)	*P* value	NCT (n=80)	NCRT (n=80)	S+CRT (n=80)	*P* value
Clinical T stage[†]								
T1	2 (1.1%)	1 (0.5%)	4 (1.2%)	<0.001	1 (1.2%)	1 (1.2%)	0 (0.0%)	0.904
T2	28 (14.9%)	13 (6.6%)	71 (21.5%)		11 (13.8%)	9 (11.2%)	10 (12.5%)	
T3	140 (74.5%)	175 (88.8%)	244 (73.9%)		63 (78.8%)	63 (78.8%)	66 (82.5%)	
T4	18 (9.6%)	8 (4.1%)	11 (3.3%)		5 (6.2%)	7 (8.8%)	4 (5.0%)	
Clinical N stage[†]								
N0[‡]	43 (22.9%)	58 (29.4%)	97 (29.4%)	0.228	25 (31.2%)	23 (28.7%)	20 (25.0%)	0.677
N+[‡]	145 (77.1%)	139 (70.6%)	233 (70.6%)		55 (68.8%)	57 (71.2%)	60 (75.0%)	
Chemotherapy regimens								
Taxane-platinum	167 (88.8%)	163 (82.7%)	226 (68.5%)	<0.001	73 (91.2%)	67 (83.8%)	54 (67.5%)	<0.001
PF	10 (5.3%)	28 (14.2%)	57 (17.3%)		2 (2.5%)	9 (11.2%)	16 (20.0%)	
No[§]	0 (0.0%)	0 (0.0%)	42 (12.7%)		0 (0.0%)	0 (0.0%)	10 (12.5%)	
Others[¶]	11 (5.9%)	6 (3.0%)	5 (1.5%)		5 (6.2%)	4 (5.0%)	0 (0.0%)	

Notes: [†]Variables used for propensity score matching. [‡]N0, no lymph node metastasis, N+, lymph node metastasis. [§]Patient did not undergo chemotherapy. [¶]Albumin paclitaxel alone or S-1 alone.

Abbreviations: NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy taxane-platinum, platinum drugs/docetaxel/paclitaxel/albumin paclitaxel; PF, platinum drugs/fluorouracil/S-1.

Table 2 Comparison of Surgical Procedures Among Three Groups Before and After Propensity Score Matching

Clinicopathologic Characteristics	Before Matching				After Matching			
	NCT (n=188)	NCRT (n=197)	Surgery (n=330)	*P* value	NCT (n=80)	NCRT (n=80)	Surgery (n=80)	*P* value
Surgical approach								
OE	139 (73.9%)	98 (49.7%)	237 (71.8%)	<0.001	59 (73.8%)	41 (51.2%)	60 (75.0%)	0.011
MIE	45 (23.9%)	95 (48.2%)	84 (25.5%)		19 (23.8%)	36 (45.0%)	19 (23.8%)	
Conversion to OE	4 (2.1%)	4 (2.0%)	9 (2.7%)		2 (2.5%)	3 (3.8%)	1 (1.2%)	
Surgical types								
Sweet	105 (55.9%)	47 (23.9%)	220 (66.7%)	<0.001	49 (61.3%)	23 (28.7%)	52 (65.0%)	<0.001
McKeown	78 (41.5%)	147 (74.6%)	103 (31.2%)		30 (37.5%)	56 (70.0%)	27 (33.8%)	
Others	5 (2.7%)	3 (1.5%)	7 (2.1%)		1 (1.2%)	1 (1.2%)	1 (1.2%)	
Lymph node dissection counts(n)								
<15	38 (20.2%)	71 (36.0%)	53 (16.1%)	<0.001	20 (25.0%)	29 (36.2%)	8 (10.0%)	<0.001
≥15	150 (79.8%)	126 (64.0%)	277 (83.9%)		60 (75.0%)	51 (63.7%)	72 (90.0%)	

Abbreviations: NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

MIE were instead converted to OE. A higher percentage of patients in the NCRT group underwent the McKeown esophagectomy compared to the NCT and S+CRT groups (70% vs 37.5% vs 33.8%, respectively; $P<0.001$ post-PSM). The NCRT group had fewer lymph node dissection counts than the other two groups ($P < 0.001$).

Surgery-Related Complications

Surgery-associated complications in the matched groups were comparable to those in the unmatched groups (as detailed in Table 3). A higher incidence of postoperative complications was observed in patients who underwent NCRT compared to those in the NCT and S+CRT groups (27.5%, 18.8% and 11.2%, respectively; $P=0.033$ after PSM). In the NCRT cohort, 14 patients (17.5%) suffered from anastomotic leakage, a significantly higher number compared to the 8 patients (10.0%) in the NCT group and 4 patients (5.0%) in the S+CRT group ($P=0.038$ post-PSM). Other postoperative complications, such as anastomotic stenosis or pulmonary complications, showed no significant differences in incidence

Table 3 Comparison of Surgery-Related Complication Among Three Groups Before and After Propensity Score Matching

Complication	Before Matching				After Matching			
	NCT (n=188)	NCRT (n=197)	Surgery (n=330)	*P* value	NCT (n=80)	NCRT (n=80)	Surgery (n=80)	*P* value
Postoperative complications								
No	144 (76.6%)	146 (74.1%)	278 (84.2%)	0.011	65 (81.2%)	58 (72.5%)	71 (88.8%)	0.033
Yes	44 (23.4%)	51 (25.9%)	52 (15.8%)		15 (18.8%)	22 (27.5%)	9 (11.2%)	
Anastomotic leakage								
No	167 (88.8%)	165 (83.8%)	310 (93.9%)	0.001	72 (90.0%)	66 (82.5%)	76 (95.0%)	0.038
Yes	21 (11.2%)	32 (16.2%)	20 (6.1%)		8 (10.0%)	14 (17.5%)	4 (5.0%)	
Anastomotic Stenosis								
No	184 (97.9%)	194 (98.5%)	320 (97.0%)	0.528	80 (100.0%)	79 (98.8%)	79 (98.8%)	0.604
Yes	4 (2.1%)	3 (1.5%)	10 (3.0%)		0 (0.0%)	1 (1.2%)	1 (1.2%)	
Pulmonary complications								
No	183 (97.3%)	191 (97.0%)	323 (97.9%)	0.798	77 (96.2%)	77 (96.2%)	79 (98.8%)	0.555
Yes	5 (2.7%)	6 (3.0%)	7 (2.1%)		3 (3.8%)	3 (3.8%)	1 (1.2%)	
Cardiac complications								
No	187 (99.5%)	193 (98.0%)	327 (99.1%)	0.333	80 (100.0%)	79 (98.8%)	80 (100.0%)	0.366
Yes	1 (0.5%)	4 (2.0%)	3 (0.9%)		0 (0.0%)	1 (1.2%)	0 (0.0%)	
Wound infection								
No	185 (98.4%)	194 (98.5%)	327 (99.1%)	0.738	79 (98.8%)	79 (98.8%)	79 (98.8%)	1.000
Yes	3 (1.6%)	3 (1.5%)	3 (0.9%)		1 (1.2%)	1 (1.2%)	1 (1.2%)	
Hoarseness								
No	187 (99.5%)	195 (99.0%)	326 (98.8%)	0.75	80 (100.0%)	78 (97.5%)	79 (98.8%)	0.363
Yes	1 (0.5%)	2 (1.0%)	4 (1.2%)		0 (0.0%)	2 (2.5%)	1 (1.2%)	
Others								
No	181 (96.3%)	193 (98.0%)	323 (97.9%)	0.469	79 (98.8%)	77 (96.2%)	78 (97.5%)	0.599
Yes	7 (3.7%)	4 (2.0%)	7 (2.1%)		1 (1.2%)	3 (3.8%)	2 (2.5%)	

Abbreviations: NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy.

among the three groups, both before and after matching. Anastomotic stenosis is defined as a narrowing at the site of the anastomosis and adjacent areas, which is not due to tumor recurrence at the anastomosis but is caused by the proliferation of granulation tissue or scarring around the anastomosis. It is characterized by a diameter of less than 1 cm at the narrowed section when assessed endoscopically, or the inability of a standard endoscope (with a diameter of about 1 cm) to pass through, often accompanied by varying degrees of dysphagia.[13]

Pathology

The rate of successful R0 resections across all three groups demonstrated similarity (NCT 97.5%, NCRT 98.7%, and S+CRT 96.2%, *P*=0.599 post-PSM), consistent with the cohort prior to matching. Prior to matching, incidences of neural and lymphovascular invasion were significantly lower in the NCRT group (*P*<0.001). However, post-matching, there were no significant differences in neural invasion across the groups (*P*=0.101). Further details can be found in Table 4.

Pathological differences between NCRT and NCT groups are detailed in Table 5. Compared to the NCT group, the NCRT group showed a higher rate of pCR. Post-matching, pCR rates were 35% for NCRT and 2.5% for NCT (*P*<0.001). The TRG 0 rate for the primary tumor was 48.8% in the NCRT cohort, significantly higher than the NCT cohort (*P*<0.001 post-PSM). Correspondingly, patients receiving NCRT demonstrated significantly higher rates of ypT0/Tis (46.2% vs 8.8%; *P*<0.001, post-PSM) and ypN0 (78.8% vs 45%; *P*<0.001, post-PSM) compared to those in the NCT cohort. The pathological results were consistent in both matched and unmatched NCRT and NCT cohorts.

Table 4 Comparison of Pathological Outcomes Among Three Groups Before and After Propensity Score Matching

Pathological Outcomes	Before Matching				After Matching			
	NCT (n=188)	NCRT (n=197)	Surgery (n=330)	*P* value	NCT (n=80)	NCRT (n=80)	Surgery (n=80)	*P* value
R0 resection								
N0	5 (2.7%)	4 (2.0%)	9 (2.7%)	0.876	2 (2.5%)	1 (1.3%)	3 (3.8%)	0.599
Yes	183 (97.3%)	193 (98%)	321 (97.3%)		78 (97.5%)	79 (98.7%)	77 (96.2%)	
Neural invasion								
N0	138 (73.4%)	173 (87.8%)	282 (85.5%)	<0.001	59 (73.8%)	69 (86.2%)	67 (83.8%)	0.101
Yes	50 (26.6%)	24 (12.2%)	48 (14.5%)		21 (26.2%)	11 (13.8%)	13 (16.2%)	
LVSI								
N0	160 (85.1%)	190 (96.4%)	286 (86.7%)	<0.001	71 (88.8%)	77 (96.2%)	63 (78.8%)	0.003
Yes	28 (14.9%)	7 (3.6%)	44 (13.3%)		9 (11.2%)	3 (3.8%)	17 (21.2%)	

Abbreviations: NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy; LVSI, lymphovascular invasion.

Table 5 Comparison of Pathological Outcomes Between the NCT Group and NCT Group Before and After Propensity Score

Pathological Outcomes	Before Matching			After Matching		
	NCT (n=188)	NCRT (n=197)	*P* value	NCT (n=80)	NCRT (n=80)	*P* value
Pathological response						
Non-pCR	181 (96.3%)	114 (57.9%)	<0.001	78 (97.5%)	52 (65.0%)	<0.001
pCR	7 (3.7%)	83 (42.1%)		2 (2.5%)	28 (35.0%)	
TRG						
0	12 (6.4%)	102 (51.8%)	<0.001	5 (6.2%)	39 (48.8%)	<0.001
1	17 (9.0%)	26 (13.2%)		4 (5.0%)	8 (10.0%)	
2	72 (38.3%)	43 (21.8%)		30 (37.5%)	20 (25.0%)	
3	87 (46.3%)	26 (13.2%)		41 (51.2%)	13 (16.2%)	
ypT stage						
T0/Tis	15 (8.0%)	98 (49.7%)	<0.001	7 (8.8%)	37 (46.2%)	<0.001
T1	9 (4.8%)	13 (6.6%)		1 (1.2%)	3 (3.8%)	
T2	37 (19.7%)	32 (16.2%)		14 (17.5%)	11 (13.8%)	
T3	119 (63.3%)	50 (25.4%)		53 (66.2%)	27 (33.8%)	
T4	8 (4.3%)	4 (2.0%)		5 (6.2%)	2 (2.5%)	
ypN stage						
N0	73 (38.8%)	155 (78.7%)	<0.001	36 (45.0%)	63 (78.8%)	<0.001
N1	67 (35.6%)	29 (14.7%)		28 (35.0%)	13 (16.2%)	
N2	34 (18.1%)	10 (5.1%)		11 (13.8%)	3 (3.8%)	
N3	14 (7.4%)	3 (1.5%)		5 (6.2%)	1 (1.2%)	

Abbreviations: NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; pCR, complete pathologic response; TRG, tumor regression grade.

OS and DFS

In the cohort under study, the median duration of follow-up was 19.3 months for the NCRT group, with a range from 4 to 66.9 months; 31.45 months for the NCT group, with the duration spanning 2 to 68.4 months; and 20.3 months for the S+CRT group, with a follow-up interval extending from 3 to 90.1 months prior to the initiation of the matching process. The NCT group exhibited a median OS of 47.7 months, with a 95% confidence interval (CI) of 32.8 months to not applicable (NA). This was significantly higher than the 26.3 months median OS observed in the S+CRT group (95% CI:

24.2–28.4 months). As for the median DFS, it was 27.8 months in the NCT group (95% CI: 18.7–43.1 months), compared to 14.6 months in the S+CRT group (95% CI: 12.0–18.7 months). For the NCRT group, the median OS and DFS could not be calculated, with the 95% confidence intervals being 55.9 months to NA and 38.9 months to NA, respectively. There were significant differences in the 5-year OS and DFS (P<0.0001 for OS and P<0.0001 for DFS) across the non-matched groups (Figure 1A and B).

Post-matching, the median follow-up duration was 20.6 months (ranging between 4 and 66.9 months) in the NCRT cohort, 31.8 months (from 7.5 to 68.4 months) in the NCT cohort, and 19.8 months (between 3 and 77.3 months) in the S+CRT cohort. The median OS for the S+CRT group was 30.4 months, with a 95% CI of 21.3 months to NA. In contrast,

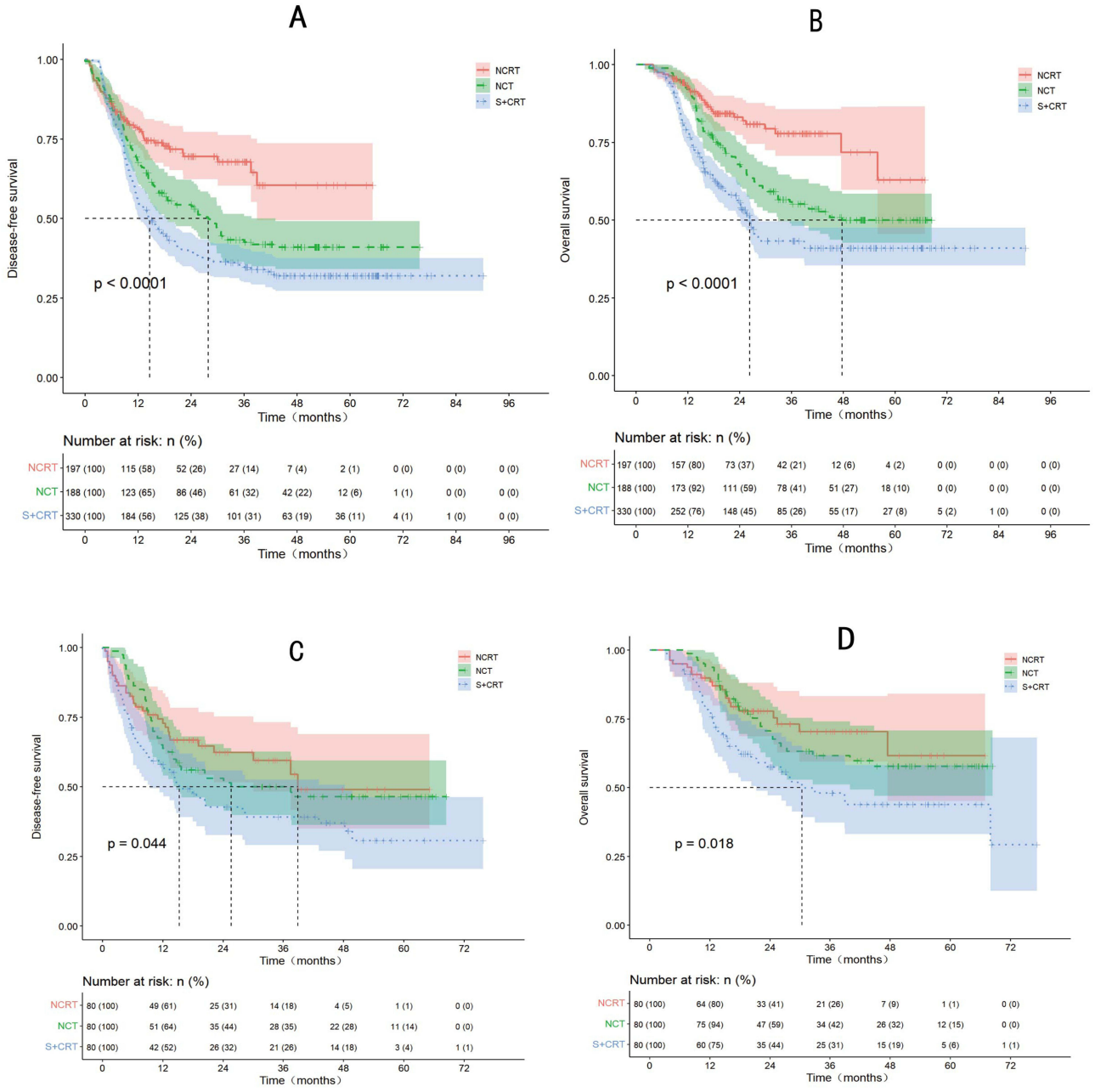

Figure 1 Unmatched Kaplan-Meier survival analysis of DFS (**A**) and OS (**B**) among NCT, NCRT and S+CRT groups. Propensity-matched Kaplan-Meier survival analysis of DFS (**C**) and OS (**D**) among NCT, NCRT and S+CRT groups.

Abbreviations: OS, overall survival; DFS, disease-free survival; NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy.

Table 6 Multivariate Analyses of Prognostic Factors Related to OS and DFS Before Propensity Score

Clinical Characteristics	OS		DFS	
	HR (CI%)	*P* value	HR (CI%)	*P* value
Therapy mode				
S+CRT†	1.58 (1.01, 2.45)	0.043	1.37 (0.95, 1.96)	0.090
NCT†	0.96 (0.62, 1.49)	0.858	0.80 (0.56, 1.15)	0.226
Covariates				
Age (< 60 vs ≥ 60)	1.28 (0.98, 1.66)	0.067	1.08 (0.86, 1.35)	0.510
Sex (M vs F)	0.69 (0.48, 0.99)	0.045	0.82 (0.60, 1.13)	0.221
Smoking (Yes vs No)	1.07 (0.80, 1.43)	0.651	1.06 (0.82, 1.36)	0.661
Alcohol (Yes vs No)	1.09 (0.82, 1.45)	0.542	0.93 (0.73, 1.20)	0.584
Tumor localization (upper vs middle, lower)	0.67 (0.45, 1.01)	0.055	0.65 (0.45, 0.92)	0.017
Surgical approach (OE vs MIE)	1.19 (0.87, 1.64)	0.282	1.08 (0.82, 1.43)	0.569
Surgical types (Sweet vs McKeown)	0.74 (0.54, 1.02)	0.064	0.94 (0.71, 1.23)	0.636
Lymph node dissection counts (< 15 vs ≥ 15)	0.86 (0.64, 1.17)	0.338	0.90 (0.69, 1.18)	0.467
(y)pT stage (T0 vs T1, T2, T3, T4)	3.59 (1.68, 7.68)	0.001	3.04 (1.74, 5.30)	<0.001
(y)pN stage (N0 vs N1, N2, N3)	1.78 (1.34, 2.37)	<0.001	1.99 (1.54, 2.56)	<0.001
Clinical T stage (T1, T2 vs T3, T4)	1.19 (0.86, 1.65)	0.284	1.18 (0.89, 1.58)	0.254
Clinical N stage (N0 vs N +)	1.24 (0.91, 1.68)	0.174	1.04 (0.80, 1.35)	0.780
Neural invasion (Yes vs No)	1.29 (0.94, 1.76)	0.113	1.15 (0.88, 1.52)	0.305
LVSI (Yes vs No)	1.30 (0.91, 1.86)	0.151	1.23 (0.89, 1.68)	0.209

Note: †Use NCRT as the reference.

Abbreviations: OS, overall survival; DFS, disease-free survival; HR, hazards ratio; CI, confidence interval; M, male; F, female; NCRT, neoadjuvant chemoradiotherapy; NCT, neoadjuvant chemotherapy; S+CRT, surgery followed by chemoradiotherapy; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

the median OS remained undefined for both the NCRT group (95% CI: 47.5 months to NA) and the NCT group (95% CI: 39.9 months to NA). Regarding the median DFS, it was recorded as 38.9 months (95% CI: 30.0 months to NA) for the NCRT group, 25.6 months (95% CI: 14.7 months to NA) for the NCT group, and 15.3 months (95% CI: 9.4 to 48.2 months) for the S+CRT group. There were statistically significant differences in the 5-year OS and 5-year DFS across the three groups (P=0.02 and P=0.04, respectively) (Figure 1C and D).

Independent predictors for OS and DFS were identified using the Cox proportional hazards model prior to matching (Table 6). Multivariate analysis revealed that the surgery followed by chemoradiotherapy was a significant independent factor associated with poorer OS compared to NCRT. Furthermore, postoperative pathological T and N stages surfaced as substantial independent predictors for both OS and DFS ($P < 0.001$).

Discussion

A comprehensive, surgery-focused treatment is standard for locally advanced resectable ESCC, including either preoperative neoadjuvant treatments like NCRT and NCT or surgery followed by adjuvant therapies (chemotherapy/radiotherapy). On the one hand, CROSS[3] trial from the Netherlands in 2012 and the NEOCRTEC5010[4] study from China in 2018 have offered significant evidence for the application of NCRT in resectable ESCC. Prospective phase III clinical trials JCOG1109NExT[9] and CMISG1701[10] concluded that surgical resection after NCT and NCRT for resectable EC were equivalent in efficacy. The 2022 CSCO Esophageal Cancer Treatment Guidelines of China recommend adding NCT for resectable EC, specifically for stages cT1b-cT2N+ or cT3-cT4a any N.[14] However, it remains uncertain whether NCT can supplant the treatment mode of NCRT in China. Both NCRT and NCT are recommended as first-line treatments for locally advanced resectable ESCC, yet the optimal strategy remains a subject of debate. On the other hand, although preoperative chemoradiotherapy followed by surgery is recognized as an effective strategy for EC treatment, there are few studies specifically addressing the impact of the order of EC surgery and chemoradiation on prognosis, with

conflicting results. Hong et al[15] through analysis of the Surveillance, Epidemiology, and End Results database proved that preoperative chemoradiotherapy is superior to postoperative chemoradiotherapy for locally advanced EC. However, prospective trials by Lv et al[16] and propensity-matched studies by Hsu et al[11] have indicated that preoperative and postoperative chemoradiation offer similar survival benefits for patients with locally advanced ESCC. Whether neoadjuvant chemoradiation and adjuvant postoperative chemoradiotherapy are equivalent for ESCC remains a question worthy of further investigation. Multimodal therapy for locally advanced ESCC is currently the best treatment strategy. The optimal approach for patients with EC continues to be a topic of discussion, as only a handful of studies have compared the results of resectable ESCC patients treated with NCRT followed by surgery, NCT followed by surgery, or surgery complemented with adjuvant chemoradiotherapy. We carried out a PSM study to examine the clinicopathological features and survival outcomes of patients treated with NCRT, NCT, and surgery followed by adjuvant chemoradiotherapy. Our findings highlighted the 5-year DFS and OS advantage of neoadjuvant therapy followed by surgery over surgery combined with adjuvant chemoradiotherapy but also found that neoadjuvant therapy was linked with an elevated rate of postoperative anastomotic leakage, both before and after PSM.

Our study is retrospective in nature, and all our patients are diagnosed with locally advanced resectable ESCC. We utilized PSM to ensure balanced baseline characteristics among the three groups. Notably, prior to matching, we observed a higher proportion of patients aged under 60, and more with tumors located in the lower esophagus, within the NCRT group. This may reflect surgical concerns about complications, including anastomotic fistulas. Such complications might be exacerbated by radiation-induced fibrosis in the mid-to-upper esophagus. The decision regarding the clinical treatment regimen was primarily based on a multidisciplinary team (MDT) approach. Each case was discussed within a multidisciplinary oncology team, which consisted of surgical oncologists, gastrointestinal medical oncologists, radiation oncologists, and radiologists. This team-based approach guaranteed the selection of the most suitable individualized treatment plans leveraging collective expertise. For instance, patients with esophageal ulcers might choose between neoadjuvant therapy or direct surgery. Furthermore, patient preference played a role in the treatment options. After reviewing the potential benefits, risks, and side effects of each treatment option, some patients may express a preference that was considered.

NCRT continues to be a standard treatment for resectable, locally advanced ESCC. Yet, a significant proportion of ESCC patients in China opt for surgery, and the Chinese guidelines recommend postoperative adjuvant chemoradiotherapy for patients at the pT3-4aN0 or pN+ stage.[8] Based on these guidelines, a PSM study[17] revealed that postoperative radiotherapy was significant association with improved OS and DFS in pT3N0M0 ESCC patients. Therefore, in our research, patients with pT3N0M0 received only postoperative radiotherapy, while those with pT4 or N+ were treated with postoperative adjuvant chemoradiotherapy. The 5-year DFS and OS were significantly higher in patients undergoing preoperative chemoradiotherapy compared to those receiving postoperative chemoradiotherapy. Yu et al[18] supported this, showing that preoperative radiotherapy improved 5-year OS relative to postoperative radiotherapy in TNM stage II/III ESCC patients. The efficacy of adjuvant therapy for ESCC is still under debate due to the absence of high-quality randomized trials. Several retrospective studies[19–24] have evaluated the role of adjuvant therapy in locally advanced operable ESCC, yielding mixed results concerning DFS and OS. Li et al[19] found that adding postoperative chemoradiotherapy in pN+ ESCC patients correlated with increased in 3-year DFS and OS. A meta-analysis[20] involving 8198 patients suggested that postoperative radiotherapy may improve DFS and reduce the risk of locoregional recurrence in ESCC patients. Similarly, Zeng et al[21] reported that postoperative radiotherapy lowered the locoregional recurrence rate in TNM stage III ESCC patients. Song et al[22] observed that postoperative chemoradiotherapy significantly reduced distant metastasis compared to postoperative radiotherapy in pN+ stage ESCC patients. Conversely, research by Zou et al[23] and Li et al[24] found no significant differences in locoregional recurrence or distant metastasis between patients receiving postoperative chemoradiotherapy or postoperative radiotherapy. Future high-quality prospective studies are necessary to establish the most effective postoperative adjuvant strategy for ESCC patients.

The combination of surgery and adjuvant chemoradiotherapy has shown limited effectiveness in prolonging OS and DFS for patients with locally advanced ESCC. Notably, neoadjuvant therapy offers improved outcomes, although these benefits carry associated risks. A randomized clinical trial[25] revealed a 9.6% incidence of postoperative anastomotic leakage in the NCRT group and an 11.1% incidence in the NCT group among patients with locally advanced ESCC. Our

retrospective PSM study corroborated these findings, showing a higher incidence of postoperative anastomotic leakage in the neoadjuvant therapy group (NCRT, 17.5%; NCT, 10%) compared to the surgery plus chemoradiotherapy (S+CRT) group (5%). Interestingly, the incidence of leakage in the neoadjuvant treatment group was slightly lower than that of the surgery-alone group in two large phase III clinical studies[3,4] of CROSS and NEOCRTEC5010 (22.3% vs 29.8% and 8.6% vs 12.3%, respectively). Furthermore, a report[26] by the Society of Thoracic Surgeons, incorporating data from 7595 esophagectomies, concluded that 10.4% of patients in the surgery group and 11.2% in the neoadjuvant radiation group experienced anastomotic leak. There was no statistically significant difference between the groups, although the database lacked detailed information on the specific chemotherapy type and radiation dose. These results are inconsistent, and our experience suggests that the risk of leakage increases when the anastomosis is located at the irradiation site, with a higher dose potentially correlating with increased risk.[27,28] Commonly, surgeons opine that neoadjuvant therapy might compromise the postoperative overall health of ESCC patients, potentially leading a higher incidence of anastomotic fistulas.

In our retrospective study's subgroup analysis, we noted significant differences in TRG rates of the primary lesion ($P < 0.001$) and pCR rates ($P < 0.001$) between the NCRT and NCT groups. The 5-year OS rate in the NCRT group indicated a potential survival advantage over the NCT group, although this was not statistically significant post-matching. These results are consistent with the findings of the multicenter phase III POET[29] and NeoRes[30] trials. However, the applicability of these trials' results was somewhat restricted, as they mainly included patients with adenocarcinomas. A randomized clinical trial, CMISG1701, which compared these two preoperative therapies utilizing MIE for locally advanced resectable ESCC, concluded that the nCRT group exhibited a higher pCR rate (35.7% vs 3.8%; $P < 0.001$) than the nCT group.[10] However, due to the brief follow-up period, it remains unclear whether a superior pCR could yield an OS benefit for ESCC patients. Our study provides further insights on this matter. Distinctively, while the CMISG1701 study only evaluated ESCC patients at the cT3-4aN0-1M0 stage, we extended our criteria to include patients at stage N2-3 ESCC, accommodating clinical demands.

Our study has certain limitations. The primary limitation was its retrospective nature; despite our efforts to enhance comparability between groups via PSM, inherent limitations of this study design remain. Secondly, the surgical methods and types were not evenly distributed across the groups. The NCRT group had a higher proportion of patients undergoing MIE and McKeown procedure, largely due to the increased patient intake post-MIE. Nonetheless, current studies[31–34] affirms that MIE yields comparable long-term survival outcomes to OE for treating localized ESCC. Additionally, our Cox proportional hazards model identified that the surgical approach and type did not independently affect OS and DFS pre-matching. Moreover, there was inconsistency in the chemotherapy regimens across the three groups, and differences in adjuvant therapy were noted between the NCRT and NCT groups. To validate our findings, a multicenter, prospective randomized controlled trial is necessary. Given the rapid advancements in immunotherapy, the management strategies for locally resectable advanced ESCC now demand personalized selection and multidisciplinary collaboration.

Conclusion

In conclusion, preoperative neoadjuvant therapy tends to improve the prognosis of resectable ESCC more effectively than postoperative adjuvant therapy, but it requires careful monitoring for potential complications. Personalizing neoadjuvant treatment strategies to each patient's individual needs, considering their personal preferences and the expertise of a multidisciplinary team, is a more appropriate approach.

Data Sharing Statement

The supporting data for this study can be procured from the corresponding author, provided a reasonable request is made.

Ethical Approval and Consent to Participate

This study has been approved by the Ethics Committee of Cancer Hospital Affiliated to Shandong First Medical University (number: SDTHEC2023004019). As the research was retrospective, there was no requirement for patient consent. We declare that patients' information will be kept confidential and that we adhere to the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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