Comparative Study - Retrospective Cohort

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Comparison of long-term survival of neoadjuvant therapy plus surgery versus upfront surgery and the role of adjuvant therapy for T1b-2N0-1 esophageal cancer: a population study of the SEER database and Chinese cohort

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Background: For stage T1b-2N0-1 esophageal cancer, the impact of neoadjuvant therapy plus surgery (NS), surgery alone (SA), and surgery plus adjuvant therapy (ST) on cancer-specific survival (CSS) and overall survival (OS) is uncertain.

Methods: Stage T1b-2N0-1 esophageal cancer patients from the SEER database and two Chinese cancer centers were included in this study. The Kaplan–Meier method was used to plot survival curves, which were compared using the log-rank test. Propensity score matching was used to equalize differences between the groups. Cox proportional hazards regression models were used to analyze prognostic factors. A nomogram for OS was developed after screening the variables using the Cox proportional hazards regression model and the least absolute shrinkage and selection operator. The performance of the nomogram was assessed by the Harrell concordance index (C-index), the area under the curve (AUC) of the receiver operating characteristic curve, calibration plots, and decision curve analysis.

Results: After propensity score matching analysis, the 3-year CSS and OS rates in the NS group compared to the SA group were 80.3% versus 62.1% ($P = 0.016$) and 75.8% versus 55.5% ($P = 0.006$), the 3-year CSS and OS rates in the NS group compared to the ST group were 71.3% versus 68.3% ($P = 0.560$) and 69.8% versus 62.9% ($P = 0.330$), the 3-year CSS and OS rates in the SA group compared to the ST group were 54.6% versus 66.7% ($P = 0.220$) and 50.2% versus 57.9% ($P = 0.290$), respectively. The predictive nomogram for OS in T1b-2N0-1 patients ultimately incorporated five clinicopathological variables: T stage, N stage, age, examined lymph nodes, and therapy modality. The nomogram C-index for predicting OS was 0.648, 0.663, and 0.666 in the training group, external validation group-1, and external validation group-2, respectively. The 1-year, 3-year, and 5-year predicted AUC values of the OS prediction model were 0.659, 0.639, and 0.612 for the training group, and 0.786, 0.758, and 0.692 for validation group-1, and 0.805, 0.760, and 0.693 for validation group-2, respectively.

Conclusion: For patients with stage T1b-2N0-1 esophageal cancer, neoadjuvant therapy significantly improves prognosis compared to surgery alone, those presenting with positive lymph nodes after upfront surgery can achieve survival benefits from adjuvant therapy.

Keywords: esophageal cancer, neoadjuvant therapy, nomogram, surgery, survival

Introduction

Esophageal cancer is a tumor of the digestive system with the 7th and 6th highest incidence and mortality rates in the world, respectively[1,2]. Patients with esophageal cancer often experience impaired swallowing function and a significantly reduced quality of life. The histologic classification of esophageal cancer mainly

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includes squamous cell carcinoma and adenocarcinoma, the distribution of which is highly related to ethnicity, smoking and drinking habits, and dietary patterns[3].

Due to the superior efficacy of neoadjuvant therapy plus surgery (NS) in the treatment of locally advanced esophageal cancer[4–6], some researchers have started to investigate the potential benefits of NS in patients with early-stage disease[7–11]. The V1 version of the 2020 National Comprehensive Cancer Network (NCCN) Guidelines for Esophageal Cancer and Esophagogastric Junction Cancer introduced two changes to the treatment of early-stage esophageal cancer compared to the previous version. The first change involved modifying the definition of well-differentiated cT1b-2 patients suitable for priority surgery from <2 cm to <3 cm. The second change recommended, for the first time, that patients with cT2N0 (vascular infiltration, ≥ 3 cm, or poorly differentiated) should receive NS as the primary treatment[12].

The NCCN guidelines for the preferred treatment of cT1b-2 esophageal cancer have remained virtually unchanged from 2020 to the present. Some scholars believe that NS has limited benefits in early-stage esophageal cancer[10,11,13], but some studies have reported that NS significantly improves disease-free survival and overall survival (OS) in stage I and II esophageal cancer[9,14–16]. There is no consensus on the efficacy of adjuvant therapy in T1b-2N0-1 esophageal cancer with poor prognostic factors. The objective of this study was to compare the survival outcomes of three treatment regimens and to develop a nomogram for OS in patients with stage T1b-2N0-1 esophageal cancer.

HIGHLIGHTS

- Patients with stage T1b-2N0-1 esophageal cancer significantly benefit from neoadjuvant therapy compared to surgery alone.
- No significant difference in the efficacy of neoadjuvant therapy compared to postoperative adjuvant therapy in patients with stage T1b-2N0-1 esophageal cancer.
- Patients presenting with positive lymph nodes after upfront surgery are a suitable population to receive adjuvant therapy for stage T1b-2N0-1 esophageal cancer.

Methods

Patients

The data for this study was obtained from the Surveillance, Epidemiology, and End Results (SEER) 17 Registries Research Plus Data (SEER*stat 8.4.2). The study population consisted of patients with stage T1b-2N0-1 esophageal cancer between 2004 and 2019. Inclusion criteria included: (a) histologically confirmed esophageal cancer; (b) clinical or pathologic staging of T1b-2N0-1 and undergoing esophagectomy; (c) receiving neoadjuvant therapy with cT1b-2N0-1; (d) tumor located in the thoracic segment; (e) first primary cancer. Exclusion criteria included patients with distant metastases, fewer than one examined lymph node, missing essential clinicopathologic information, and survival of three months or less. The stages of all esophageal cancer patients were reclassified according to the American Joint Committee on Cancer Manual, 8th edition.

The inclusion and exclusion criteria in the external validation were consistent with those of the two institutes (Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University). We conducted a retrospective study of patients with esophageal cancer who underwent surgery between January 2014 and March 2022 and met the selection criteria at both institutes, with follow-up until October 2023. Patients at both hospitals provided detailed information on vascular infiltration and nerve invasion. The study was approved by the relevant review board, which granted a waiver for signing the patients' individual consent forms.

All the patients were divided into three groups: NS group, surgery alone (SA) group, and surgery plus adjuvant therapy (ST) group. In the SEER database, neoadjuvant treatment for the NS group included radiotherapy, radiochemotherapy, and chemotherapy. Patients who received neoadjuvant chemoimmunotherapy were categorized into the NS group in the Chinese cohort. Postoperative treatment for the ST group included radiotherapy, radiochemotherapy, and chemotherapy.

Survival analysis

In the survival analysis, the main observations in the SEER database were the 3-year cancer-specific survival (CSS) and OS rates, whereas, in the two-center Chinese cohort, the primary observation was the 3-year OS rate.

Construction and validation of prognostic prediction model

We developed a nomogram to predict OS in patients with T1b-2N0-1 esophageal cancer. The SEER database was used as the training group. Variables for constructing the OS rate prediction model were screened by univariate Cox regression, the least absolute shrinkage and selection operator (LASSO), and multivariate Cox regression analysis. Esophageal cancer patients from Renmin Hospital of Wuhan University and Zhongnan Hospital of Wuhan University served as external validation groups 1 and 2, respectively. The efficacy of the model was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Calibration plots were created to assess the disparity between the predicted and actual outcomes of the model. Decision curve analysis was used to demonstrate the utility of the nomogram in clinical applications.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables are presented as medians with 25th and 75th percentiles (interquartile range [IQR]). Kaplan–Meier curves and the log-rank test were used to evaluate survival. The propensity score matching (PSM) method, used as a sensitivity analysis, employed the nearest-neighbor method (without replacement; caliper set at 0.02) to select matched samples, with baseline characteristics matched in a 1:1 ratio. Characteristics that were difficult to define or were very few in number were classified in the 'other' or 'unknown' subgroups. Statistical significance was determined using a predefined two-sided alpha value of 0.05 and a 95% CI. Statistical analyses were conducted using SPSS Statistics version 26.0, and R version 4.2.0. This study has been reported according to strengthening the reporting of cohort, cross-sectional, and case–control studies in Surgery (STROCSS) (Supplemental Digital Content 1, http://links.lww.com/JS9/C863) standards[17].

Results

General clinical data

In the SEER database, 584 esophageal cancer patients were eligible for inclusion. The majority of patients were white (515/584, 88.2%), aged 65 years or older (310/584, 53.1%), male (478/584, 81.8%), with tumors located in the lower esophagus (480/584, 82.2%), diagnosed with adenocarcinoma/adenosquamous carcinoma (430/584, 73.6%), at stage T2 (454/584, 77.7%), stage N0 (361/584, 61.8%), middle grade (236/584, 40.4%), with a tumor size less than 3 cm (267/584, 45.7%), and with an examined lymph nodes (ELN) between 10 and 20 (283/584, 48.5%). The clinicopathologic variables of the different treatments are presented in Table 1.

Correlations of different therapies with prognosis in the SEER database

In the SEER database, there were 280 patient deaths, including 186 from esophageal cancer, with a median follow-up of 33 months (IQR 17–55). CSS and OS were compared between the two groups of unadjusted and PSM patients treated with NS, SA, and ST, respectively. Supplementary Table S1-4 (Supplemental Digital Content 2, http://links.lww.com/JS9/C864) displays the distribution of the unadjusted and PSM variables for the different treatment groups, while Supplementary Figure S1-4 (Supplemental Digital Content 3, http://links.lww.com/JS9/C865) illustrates the corresponding standardized mean differences.

Between the NS group and the SA group

Unadjusted survival analysis showed no significant difference between the NS group and the SA group, the 3-year CSS and OS rates were 80.2% (95% CI: 72.5–88.6%) versus 71.3% (95% CI: 66.1–77.0%) [$P = 0.140$] and 75.6% (95% CI: 67.9–84.6%) versus 64.4% (95% CI: 59.1–70.2%) [$P = 0.055$], respectively. After PSM, the 3-year CSS and OS rates in the NS group and the SA group were 80.3% (95% CI: 71.8–89.8%) versus 62.1% (95% CI: 51.6–74.6%) [$P = 0.016$] and 75.8% (95% CI: 66.9–86.0%) versus 55.5% (95% CI: 45.3–68.0%) [$P = 0.006$], respectively (Supplementary Figure S5, Supplemental Digital Content 4, http://links.lww.com/JS9/C866).

Between the NS group and the ST group

Unadjusted survival analyses showed significantly higher 3-year CSS and OS rates in the NS group compared with the ST group: 80.2% (95% CI: 72.5–88.6%) versus 64.8% (95% CI: 56.8–73.8%) [$P = 0.008$] and 75.6% (95% CI: 67.6–84.6%) versus 58.9% (95% CI: 50.9–68.0%) [$P = 0.004$], respectively. After PSM, there was no significant difference in survival between the two groups, with a 3-year CSS and OS rates were 71.3% (95% CI: 60.9–83.5%) versus 68.3% (95% CI: 57.4–81.2%) [$P = 0.560$] and 69.8% (95% CI: 59.3–82.2%) versus 62.9% (95% CI: 51.9–76.2%) [$P = 0.330$], respectively (Supplementary Figure S6, Supplemental Digital Content 4, http://links.lww.com/JS9/C866).

Between the SA group and the ST group

Unadjusted survival analyses showed a significant improvement in CSS in the SA group compared to the ST group, but not in OS. The 3-year CSS and OS rates in the two groups were 71.3% (95% CI: 66.1–77.0%) versus 64.8% (95% CI: 56.8–73.8%) [$P = 0.023$] and 64.4% (95% CI: 59.1–70.2%) versus 58.9% (95% CI: 50.9–68.0%) [$P = 0.190$], respectively. After PSM, there was no significant difference in survival between the SA group and the ST group, with a 3-year CSS of 54.6% (95% CI: 44.4–67.2%) versus 66.7% (95% CI: 56.5–78.8%) [$P = 0.220$] and 50.2% (95% CI: 40.3–62.6%) versus 57.9% (95% CI: 47.8–70.1%) [$P = 0.290$] for the two groups, respectively (Supplementary Figure S7, Supplemental Digital Content 4, http://links.lww.com/JS9/C866). Results were validated by a Chinese cohort population, and survival analyses are presented in

Table 1

Clinicopathologic characteristics of patients with stage T1b-2N0-1 esophageal cancer in the SEER database.

Characteristics	Total ($N = 584$, %)	NS group ($N = 101$, %)	SA group ($N = 342$, %)	ST group ($N = 141$, %)
Race				
White	515 (88.2)	87 (86.1)	301 (88.0)	127 (90.1)
Black	25 (4.3)	7 (6.9)	15 (4.4)	3 (2.1)
Other	44 (7.5)	7 (6.9)	26 (7.6)	11 (7.8)
Age (years)				
< 55	100 (17.1)	14 (13.9)	56 (16.4)	30 (21.3)
55–64	174 (29.8)	41 (40.6)	90 (26.3)	43 (30.5)
≥ 65	310 (53.1)	46 (45.5)	196 (57.3)	68 (48.2)
Sex				
Female	106 (18.2)	24 (23.8)	68 (19.9)	14 (9.9)
Male	478 (81.8)	77 (76.2)	274 (80.1)	127 (90.1)
Tumor location				
Upper	13 (2.2)	1 (1.0)	8 (2.3)	4 (2.8)
Middle	91 (15.6)	13 (12.9)	65 (19.0)	13 (9.2)
Lower	480 (82.2)	87 (86.1)	269 (78.7)	124 (87.9)
Histology				
AC/ASC	430 (73.6)	75 (74.3)	239 (69.9)	116 (82.3)
SCC	121 (20.7)	21 (20.8)	86 (25.1)	14 (9.9)
Other	33 (5.7)	5 (5.0)	17 (5.0)	11 (7.8)
T stage				
T1b	130 (22.3)	9 (8.9)	101 (29.5)	20 (14.2)
T2	454 (77.7)	92 (91.1)	241 (70.5)	121 (85.8)
N stage				
N0	361 (61.8)	51 (50.5)	276 (80.7)	34 (24.1)
N1	223 (38.2)	50 (49.5)	66 (19.3)	107 (75.9)
Grade				
Well	38 (6.5)	5 (5.0)	27 (7.9)	6 (4.3)
Middle	236 (40.4)	39 (38.6)	142 (41.5)	55 (39.0)
Poorly	200 (34.2)	40 (39.6)	101 (29.5)	59 (41.8)
Unknown	110 (18.8)	17 (16.8)	72 (21.1)	21 (14.9)
Tumor size (cm)				
< 3	267 (45.7)	30 (29.7)	185 (54.1)	52 (36.9)
≥ 3	252 (43.2)	52 (51.5)	128 (37.4)	72 (51.1)
Unknown	65 (11.1)	19 (18.8)	29 (8.5)	17 (12.1)
ELN				
< 10	148 (25.3)	24 (23.8)	91 (26.6)	33 (23.4)
10–20	283 (48.5)	57 (56.4)	152 (44.4)	74 (52.5)
> 20	153 (26.2)	20 (19.8)	99 (28.9)	34 (24.1)
Type				
Radiotherapy-containing	–	97 (96.0)	–	95 (67.4)
Chemotherapy	–	4 (4.0)	–	49 (34.8)

AC, Adenocarcinoma; ASC, Adenosquamous carcinoma; SCC, squamous cell carcinoma; ELN, examined lymph nodes; NS, neoadjuvant therapy plus surgery; SA, surgery alone; ST, surgery plus adjuvant therapy.

Supplementary File 1 (Supplemental Digital Content 5, http://links.lww.com/JS9/C867).

Subgroup analysis of adjuvant therapy

No significant difference in survival was found between the postoperative radiotherapy group and the postoperative chemotherapy group. The 3-year cancer CSS and OS rates in the two groups were 63.4% (95% CI: 53.8–74.7%) versus 66.9% (95% CI: 53.5–83.7%) [$P = 0.310$] and 57.9% (95% CI: 48.4–69.3%) versus 60.4% (95% CI: 47.2–77.2%) [$P = 0.470$], respectively. After PSM, the 3-year CSS and OS rates were 57.0% (95% CI: 40.5–80.2%) versus 67.3% (95% CI: 51.0–88.9%) [$P = 0.380$] and 54.3% (95% CI: 38.1–77.4%) versus 61.8% (95% CI: 45.7–83.7%) [$P = 0.480$], respectively (Supplementary Figure S8, Supplemental Digital Content 4, http://links.lww.com/JS9/C866). Results were validated by a Chinese cohort population, and survival analyses are presented in Supplementary File 2 (Supplemental Digital Content 6, http://links.lww.com/JS9/C868).

Forest map and subgroup survival analysis

We conducted a subgroup analysis of post-PSM patients who received various treatments to identify subgroups showing significant survival benefits (Supplementary Figure S9-11, Supplemental Digital Content 7, http://links.lww.com/JS9/C869). The results showed significant improvements in CSS in the NS group compared to the SA group in several subgroups. These factors include T2 stage (HR = 0.78, 95% CI: 0.63–0.96, $P = 0.022$), N1 stage (HR = 0.75, 95% CI: 0.58–0.97, $P = 0.027$), well or middle grade (HR = 0.55, 95% CI: 0.33–0.92, $P = 0.022$), male (HR = 0.79, 95% CI: 0.63–0.99, $P = 0.043$), adenocarcinoma and adenosquamous carcinoma (HR = 0.75, 95% CI: 0.59–0.96, $P = 0.020$), and tumor size less than 3 cm (HR = 0.49, 95% CI: 0.24–0.98, $P = 0.042$). Several subgroups of the population had a significant OS benefit, such as T2 stage (HR = 0.78, 95% CI: 0.65–0.95, $P = 0.012$), N1 stage (HR = 0.73, 95% CI: 0.57–0.93, $P = 0.011$), well or moderately differentiated (HR = 0.49, 95% CI: 0.30–0.81, $P = 0.005$), male (HR = 0.76, 95% CI: 0.62–0.93, $P = 0.007$), adenocarcinoma and adenosquamous carcinoma (HR = 0.76, 95% CI: 0.61–0.94, $P = 0.011$), tumor size ≥ 3 cm/unknown (HR = 0.78, 95% CI: 0.63–0.96, $P = 0.017$), age ≥ 65 years (HR = 0.75, 95% CI: 0.59–0.96, $P = 0.022$), ELN > 20 (HR = 0.64, 95% CI: 0.41–0.99, $P = 0.046$).

In the NS versus ST group, OS significantly improved only in the well/middle-grade population (HR = 0.33, 95% CI: 0.12–0.93, $P = 0.036$). In the ST versus SA group, only the CSS in N1 stage (HR = 0.56, 95% CI: 0.32–0.98, $P = 0.044$) showed a significant improvement; however, OS improvement was not statistically significant in the N1 stage (HR = 0.65, 95% CI: 0.40–1.04, $P = 0.072$).

Nomogram development

Variable selection

Patients from the SEER database were assigned to the training group. First, univariate Cox proportional hazards regression analysis revealed that T stage, N stage, age, ELN, grade, histology, tumor size, and therapy modality were screened as clinicopathological variables significantly associated with OS (Table 2). Secondly, significant prognostic factors for univariate Cox regression were included in the Lasso regression model to prevent overfitting. The changes in the coefficients of the variables during Lasso regression and the process of cross-validation for the optimal values of the parameter λ in the Lasso regression model are illustrated in Figure 1. The Lasso regression, with Lambda minimizing the mean squared error, screened variables such as T stage, N stage, age, ELN, grade, histology, and therapy, which were ultimately included in the multivariate Cox analysis. Multivariate Cox analysis conducted in the training group showed that T stage, N stage, age,

Table 2

Univariate and multivariate analysis of OS in patients with T1b-2N0-1 esophageal cancer in the SEER database.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Race				
White	1		—	—
Black	1.32 (0.74–2.36)	0.347	—	—
Other	0.84 (0.52–1.35)	0.462	—	—
Age (years)				
< 55	1		1	
55–64	1.29 (0.87–1.91)	0.205	1.17 (0.78–1.76)	0.438
≥ 65	1.83 (1.29–2.61)	0.001	1.64 (1.15–2.35)	0.007
Sex				
Female	1		—	—
Male	1.34 (0.96-1.87)	0.088	—	—
Tumor location				
Upper	1		—	—
Middle	0.70 (0.34–1.41)	0.315	—	—
Lower	0.53 (0.27–1.04)	0.064	—	—
Histology				
AC/ASC	1		1	
SCC	1.38 (1.05–1.83)	0.023	1.21 (0.90–1.63)	0.207
Other	1.56 (0.98–2.47)	0.060	1.13 (0.70–1.82)	0.612
T stage				
T1b	1		1	
T2	1.91 (1.22–3.01)	0.005	1.63 (1.02–2.60)	0.042
N stage				
N0	1		1	
N1	1.85 (1.46–2.34)	< 0.001	1.96 (1.48–2.59)	< 0.001
Grade				
Well	1		1	
Middle	1.39 (0.83–2.31)	0.210	1.24 (0.74–2.09)	0.418
Poorly	2.01 (1.21–3.33)	0.007	1.65 (0.97–2.79)	0.065
Unknown	1.15 (0.62–2.13)	0.664	1.15 (0.60–2.17)	0.677
Tumor size (cm)				
< 3	1		—	—
≥ 3	1.29 (1.01–1.65)	0.045	—	—
Unknown	0.74 (0.48–1.14)	0.174	—	—
ELN				
< 10	1		1	
10–20	0.73 (0.56–0.96)	0.024	0.70 (0.53–0.93)	0.012
> 20	0.70 (0.49–0.92)	0.014	0.62 (0.44–0.85)	0.003
Therapy				
SA	1		1	
ST	1.19 (0.92–1.54)	0.195	0.84 (0.62–1.14)	0.267
NS	0.64 (0.41–0.99)	0.043	0.51 (0.32–0.80)	0.003

AC, Adenocarcinoma; ASC, Adenosquamous carcinoma; SCC, squamous cell carcinoma; ELN, examined lymph nodes; NS, neoadjuvant therapy plus surgery; SA, surgery alone; ST, surgery plus adjuvant therapy.

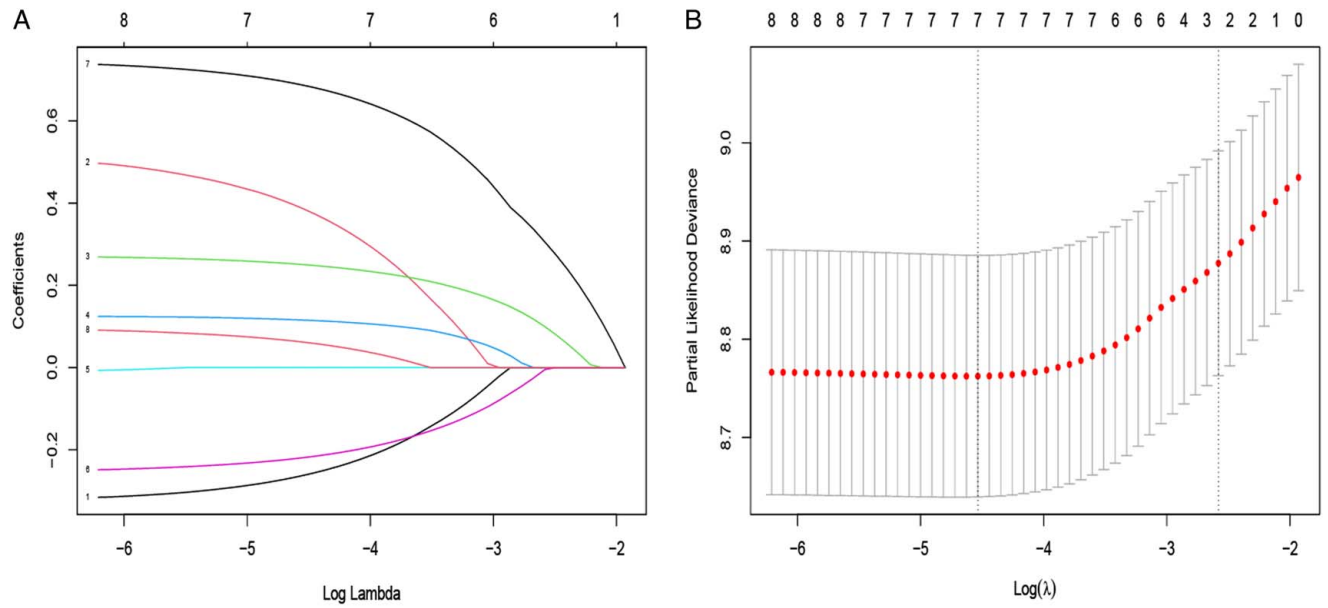

Figure 1. Screening of variables based on Lasso regression. (A) The characteristics of variable coefficient variations; (B) the selection process involves determining the optimal value of the parameter λ in the Lasso regression model using the cross-validation method.

ELN, and therapy modality were significantly associated with OS, and these factors were included in the development of the nomogram and Fig. 2.

Efficacy of the model

Two external validation groups of esophageal cancer patients from different cancer centers were used to validate the efficacy of the OS prognostic model. All the patients in the two external validation groups were Asian. In the Chinese cohort, 100 patients died, and the median follow-up time was 28 months (IQR 17–49). The Chinese cohort population was aged ≥65 years (144/323, 44.6%), male (238/323, 73.7%), with mid-thoracic tumors (204/323, 63.2%), squamous cell carcinoma (312/323, 96.6%), T2 stage (208/323, 64.4%), moderately differentiated (243/323, 75.2%), tumor size <3 cm (171/323, 52.9%), with no vascular infiltration (275/323, 85.3%), with no never invasion (292/323, 90.4%), ELN of 10–20 (145/323, 44.9%), and SA (214/323, 66.3%) predominated among patients. The distribution of specific characteristics in the two external validation groups is shown in Table 3.

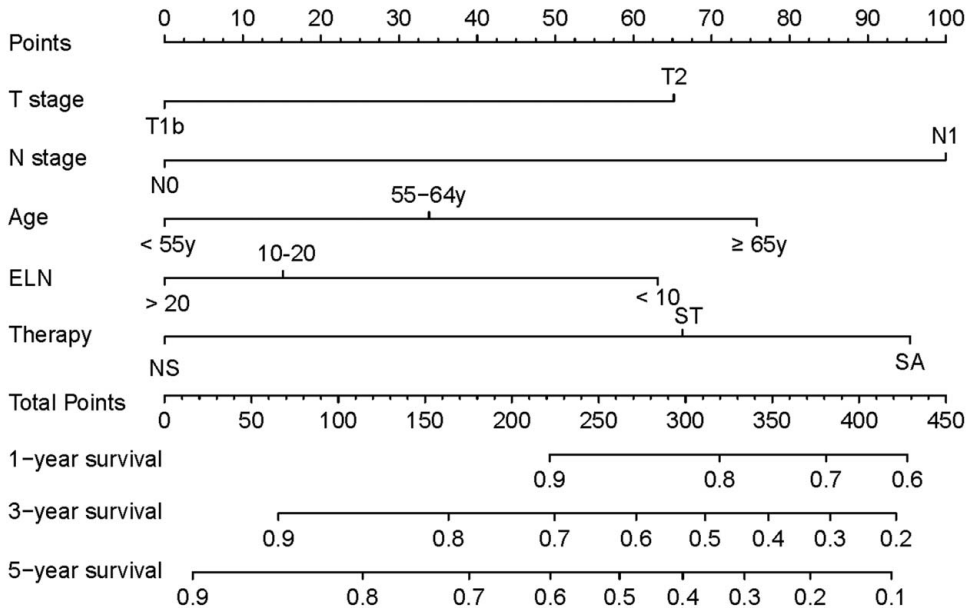

Figure 2. Nomogram of clinical variables for the prediction of overall survival rates.

The C-index of the nomogram for OS was 0.647, 0.663, and 0.666 in the SEER database, validation group-1, and validation group-2, respectively. The 1-year, 3-year, and 5-year predicted AUC values of the nomogram were 0.659, 0.639, and 0.612 for the training group, and 0.786, 0.758, and 0.692 for validation group-1, and 0.805, 0.760, and 0.693 for validation group-2, respectively (Fig. 3). To evaluate the validity of the constructed nomogram, we calibrated the graph by applying 1000 bootstrap sample corrections to both the training group and the validation groups. The dashed diagonal represents the ideal line, where the predicted probability matches the observed probability. The decision curve analysis revealed that the prognostic nomogram has strong clinical utility (Fig. 4). In conclusion, the OS prediction model performed well in both validation groups.

Table 3

Clinicopathologic characteristics of patients with stage T1b-2N0-1 esophageal cancer in the Chinese cohort.

Characteristics	Total ($N=323$, %)	Validation group-1 ($N=172$, %)	Validation group-2 ($N=151$, %)
Age (year)			
<55	54 (16.7)	35 (20.3)	19 (12.6)
55–64	125 (38.7)	70 (40.7)	55 (36.4)
≥ 65	144 (44.6)	67 (39.0)	77 (51.0)
Sex			
Female	85 (57.3)	49 (28.5)	36 (23.8)
Male	238 (73.7)	123 (71.5)	115 (76.2)
Tumor location			
Upper	10 (3.1)	10 (5.8)	0 (0.0)
Middle	204 (63.2)	104 (60.5)	100 (66.2)
Lower	109 (33.7)	58 (33.7)	51 (33.8)
Histology			
AC/ASC	5 (1.5)	4 (2.3)	1 (0.7)
SCC	312 (96.6)	163 (94.8)	149 (98.7)
Other	6 (1.9)	5 (2.9)	1 (0.7)
T stage			
T1b	115 (35.6)	70 (40.7)	45 (29.8)
T2	208 (64.4)	102 (59.3)	106 (70.2)
N stage			
N0	221 (68.4)	118 (68.6)	103 (68.2)
N1	102 (31.6)	54 (31.4)	48 (31.8)
Grade			
Well	22 (6.8)	22 (12.8)	0 (0.0)
Middle	243 (75.2)	116 (67.4)	127 (84.1)
Poorly	44 (13.6)	22 (12.8)	22 (14.6)
Unknown	14 (4.3)	12 (7.0)	2 (1.3)
Tumor size (cm)			
<3	171 (52.9)	102 (59.3)	69 (45.7)
≥ 3	141 (43.7)	62 (36.0)	79 (52.3)
Unknown	11 (3.4)	8 (4.7)	3 (2.0)
Vascular infiltration			
N0	275 (85.1)	148 (86.0)	127 (84.1)
Yes	48 (14.9)	24 (14.0)	24 (15.9)
Nerve invasion			
N0	292 (90.4)	162 (94.2)	130 (86.1)
Yes	31 (9.6)	10 (5.8)	21 (13.9)
ELN			
<10	83 (25.7)	49 (28.5)	34 (22.5)
10–20	145 (44.9)	88 (51.2)	57 (37.7)
>20	95 (29.4)	35 (20.3)	60 (39.7)
Therapy			
NS	27 (8.4)	22 (12.8)	5 (3.3)
SA	214 (66.3)	116 (67.4)	98 (64.9)
ST	82 (25.4)	34 (19.8)	48 (31.8)

AC, Adenocarcinoma; ASC, Adenosquamous carcinoma; SCC, squamous cell carcinoma; ELN, examined lymph nodes; NS, neoadjuvant therapy plus surgery; SA, surgery alone; ST, surgery plus adjuvant therapy.

Discussion

The tumor stage is one of the most crucial factors in determining treatment choices for esophageal cancer. Early diagnosis and early treatment can improve patient survival, interventional endoscopic screening aids in enhancing the detection rate of early-stage esophageal cancer[18]. Although the accuracy of endoscopic diagnostic techniques is increasing, pathologic factors such as T stage, N stage, vascular infiltration, and grade cannot be accurately assessed[8,19,20]. Unlike the efficacy of NS in advanced esophageal cancer, its effectiveness in early-stage esophageal cancer is much more controversial, with far fewer published studies available. In studies of early-stage esophageal cancer, Rice *et al*.[21] and Zhang *et al*.[7] found that the actual accuracy of EUS staging was 13 and 28%, respectively. The staging of patients with early esophageal cancer relies on the clinician's experience, and tailoring treatment decisions to individual patients increases the reliance on clinician guidance.

A study by Mann *et al*.[22] showed no significant difference in long-term survival between patients with cT1b esophageal cancer who underwent neoadjuvant chemoradiation therapy compared to upfront surgery. The 5-year OS rates were 49.4% versus 67.2%, with an HR of 1.85 (95% CI: 1.36–2.52; $P<0.05$). Subgroup Cox analysis in our study showed no significant difference in CSS (HR = 0.83, 95% CI: 0.33–2.10, $P=0.698$) and OS (HR = 0.67, 95% CI: 0.30–1.50, $P=0.329$) between patients with esophageal cancer at stage T1b who underwent NS versus SA. In a study conducted by Markar *et al*.[9], 355 patients with cT2N0M0 esophageal cancer were included, the findings revealed that compared to upfront surgery, neoadjuvant chemoradiotherapy resulted in more radical resections (99 vs. 89%, $P=0.031$) and a better 5-year overall survival rate (46 vs. 33%, $P=0.017$). Rodriguez-Quintero *et al*.[10] showed that neoadjuvant chemoradiotherapy is associated with improved survival compared to upfront surgery in cT2N0M0 esophageal cancer patients with tumor >5 cm (HR = 0.30, 95% CI: 0.17–0.36). Several studies have found that receiving induction therapy does not significantly improve the survival of cT2N0M0 patients[23–27].

Our results indicated that in the SEER database, patients with stage T1b-2N0-1 esophageal cancer showed significant improvements in CSS (HR = 0.78, 95% CI: 0.63–0.96, $P=0.019$) and OS (HR = 0.78, 95% CI: 0.65–0.93, $P=0.007$) when comparing NS to SA. The NS group showed a significant improvement in 3-year CSS rate (80.3 vs. 62.1%, $P=0.016$) and OS rate (75.8 vs. 55.5%, $P=0.006$) compared to the SA group in stage T1b-2N0-1 patients. Subgroup analyses revealed that stages T2 and N1 were populations in which neoadjuvant therapy was beneficial, resulting in significant improvements in CSS and OS. However, there was no significant difference between NS and ST in the 3-year CSS rates (71.3 vs. 68.3% $P=0.560$) and OS rates (69.8 vs. 62.9%, $P=0.330$).

After upfront surgical R0 resection, the NCCN guidelines (Version 4 for 2023) recommend adjuvant therapy for lymph node-positive or pT2 stage with adenocarcinoma, but surveillance is recommended for squamous cell carcinoma. A meta-analysis showed that postoperative radiotherapy ($N=1774$)

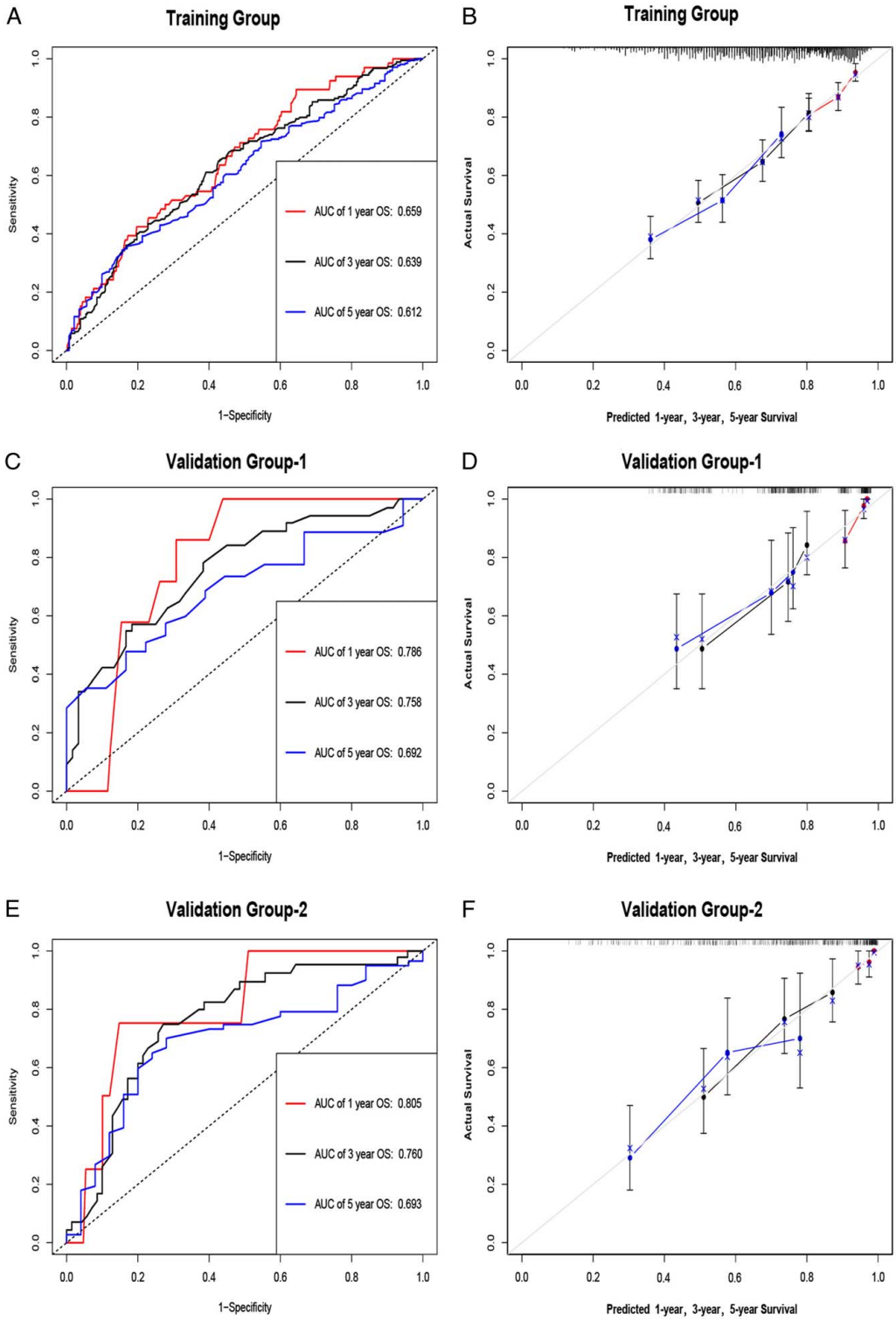

Figure 3. ROC curves (A,C,E) and calibration plots (B,D,F) for the nomogram training group, validation group-1, and validation group-2 predicting 1-year, 3-year, and 5-year OS.

significantly improved OS (HR = 0.86, 95% CI: 0.79–0.93, $P < 0.01$) and disease-free survival (HR = 0.74, 95% CI: 0.63–0.87, $P < 0.01$) compared to SA ($N = 3886$)[28]. A multi-center real-world study ($N = 4189$) by Yang W *et al.*[29] showed that N1 + stage patients were likely to benefit from the addition of adjuvant therapy compared to surgery alone. Though adjuvant therapy did not improve overall survival for N0 stage patients, adjuvant therapy improved survival in patients with stage IIb-III thoracic esophageal squamous carcinoma, with a 5-year OS and disease-free survival of 26.4 vs. 37.1% ($P = 0.002$) and 26.5 vs.

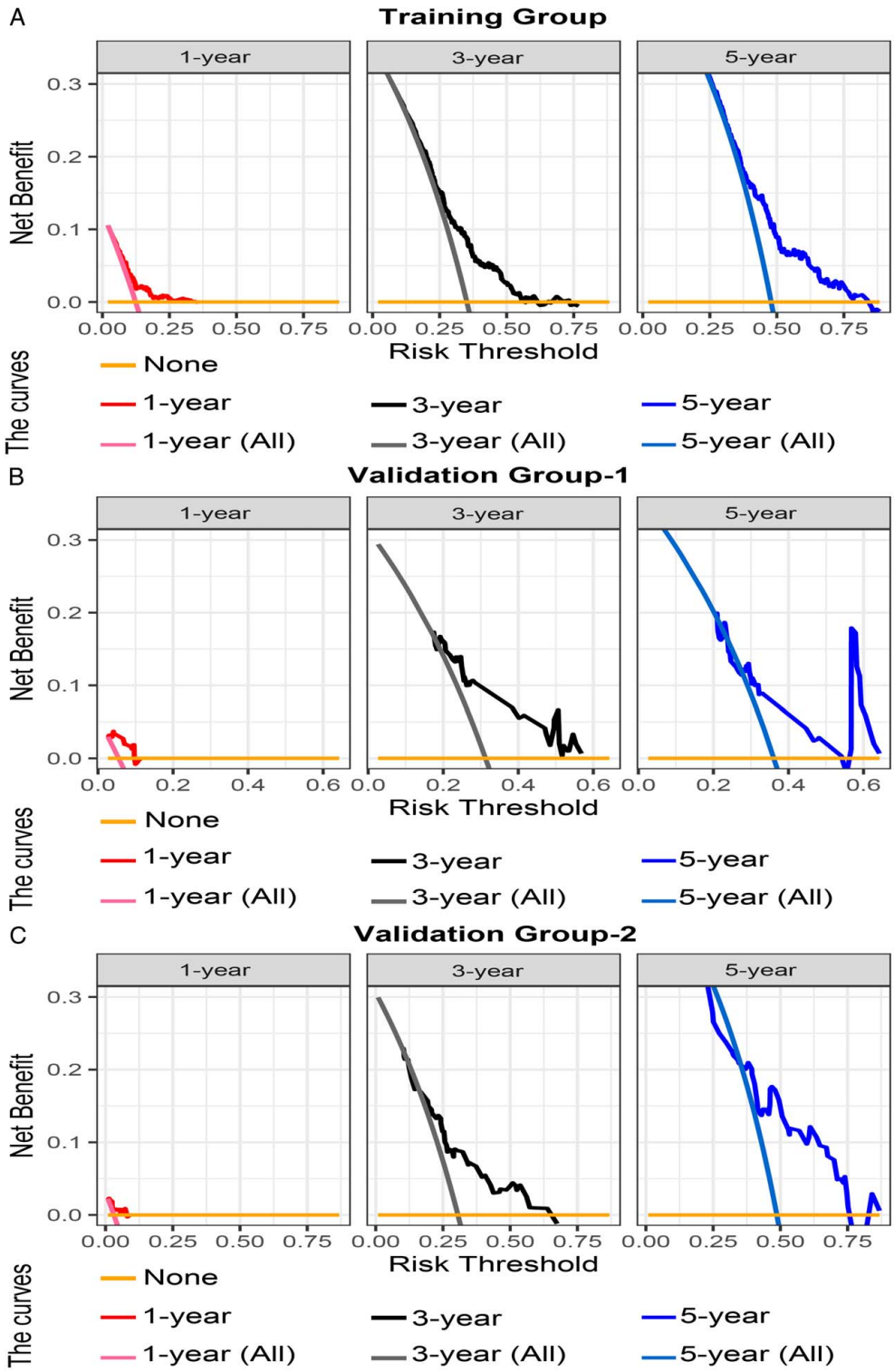

Figure 4. Decision curve analysis of the nomogram for the OS prediction of esophageal cancer patients with T1b-2N0-1 shows 1-year, 3-year, and 5-year survival benefits in the training group (A), validation group-1 (B), and validation group-2 (C). The curve indicates the net benefit of the nomogram model by summing the true positives and subtracting the false positives.

32.7% ($P = 0.035$) in the SA and ST groups, respectively, after PSM[30]. It seems that the NCCN guidelines are too conservative for the adjuvant treatment of patients with lymph node-positive esophageal squamous carcinoma.

In our study, survival analyses of patients with T1b-2N0-1 esophageal cancer in the SEER database showed significant improvement in CSS (HR = 0.56, 95% CI: 0.32–0.98, $P = 0.044$) in N1 subgroups on ST versus SA, but not significant improvement in OS (HR = 0.65, 95% CI: 0.40–1.04, $P = 0.072$). In addition, there was no significant difference in 3-year CSS rates (57.0 vs. 67.3%, $P = 0.380$) and OS rates (54.3 vs. 61.8%, $P = 0.480$) for postoperative radiotherapy compared to postoperative chemotherapy.

As demonstrated in our study, there is a cross-sectional relationship between survival, tumor size, grade, and vascular infiltration in stage T1b-2N0-1 esophageal cancer (Supplementary Figure S12-13, Supplemental Digital Content 8, http://links.lww.com/JS9/C870). For esophageal cancer patients with stage T2 or N1 are more likely to benefit from neoadjuvant therapy. We have developed and validated a nomogram for monitoring OS in patients with stage T1b-2N0-1 esophageal cancer, which could assist clinicians personalize treatment recommendations for these cohort of patients.

Our study utilized a PSM approach to mitigate intergroup bias and compared the impacts of various treatments on the survival of patients diagnosed with early-stage esophageal cancer in both the SEER database and the Chinese cohort, the results provides additional evidence of an interaction between important clinicopathological characteristics of early esophageal cancer and survival, we can scientifically maximize the value of databases by leveraging their strengths. Meanwhile, it is important to recognize the limitations of the database and consider the impact of variations in the study population's origin on the findings.

The number of patients in our study was limited, however, our analysis focused on stage T1b-2N0-1 esophageal cancer patients and found that neoadjuvant therapy can provide a survival benefit in this patient cohort. We believe that a prospective, randomized clinical trial comparing NS with SA in patients with T1b-2N0-1 esophageal cancer is necessary to further validate these findings.

Conclusions

For patients with stage T1b-2N0-1 esophageal cancer, neoadjuvant therapy significantly improves long-term survival compared to surgery alone but fails to improve survival outcomes compared to adjuvant therapy, those presenting with positive lymph nodes after upfront surgery can achieve survival benefits from adjuvant therapy.

Ethical approval

After reviewed by the Ethical Committee of Renmin Hospital of Wuhan University (WDRY2022-K078), our study (RENMIN-226) was approved exemption from signing informed consent.

Consent

Immunity from informed consent. No adverse effects on study subjects

Source of funding

None.

Author contribution

L.X.: conceptualization, writing – original draft, investigation, prepared all the figures and tables, and drafted the manuscript; W.S.: supervision and writing – review and editing; Z.L. and Y. C.: resources, investigation, methodology, and formal analysis; Z.H. and H.Q.: resources, investigation, validation, and formal analysis; Y.C. and J.W.: conceptualization, supervision, and writing – review and editing. All the authors reviewed and approved the final manuscript.

Conflicts of interest disclosure

All authors declare that they have no competing interests.

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Guarantor

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Data availability statement

The data used and analyzed in this study are available from the corresponding author.

Provenance and peer review

None.

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References

[1] Sung H, Ferlay J, Siegel RL, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.
[2] Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. Gastroenterology 2018;154:360–73.
[3] Hongo M, Nagasaki Y, Shoji T. Epidemiology of esophageal cancer: orient to Occident. Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 2009;24:729–35.
[4] Eyck BM, van Lanschot JJB, Hulshof MCCM, *et al*. Ten-year outcome of neoadjuvant chemoradiotherapy plus surgery for esophageal cancer: the randomized controlled CROSS Trial. J Clin Oncol 2021;39:1995–2004.
[5] Shapiro J, van Lanschot JJB, Hulshof MCCM, *et al*. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16:1090–8.
[6] Yang H, Liu H, Chen Y, *et al*. Long-term efficacy of neoadjuvant chemoradiotherapy plus surgery for the treatment of locally advanced

esophageal squamous cell carcinoma: the NEOCRTEC5010 randomized clinical trial. JAMA Surg 2021;156:721–9.
[7] Zhang JQ, Hooker CM, Brock MV, *et al*. Neoadjuvant chemoradiation therapy is beneficial for clinical stage T2N0 esophageal cancer patients due to inaccurate preoperative staging. Ann Thorac Surg 2012;93:429–35.
[8] Hardacker TJ, Ceppa D, Okereke I, *et al*. Treatment of clinical T2N0M0 esophageal cancer. Ann Surg Oncol 2014;21:3739–43.
[9] Markar Sheraz R, Goense L, Visser E, *et al*. Role of neoadjuvant chemoradiotherapy in clinical T2N0M0 esophageal cancer: a population-based cohort study. Eur J Surg Oncol 2018;44:620–5.
[10] Rodriguez-Quintero JH, Kamel MK, Jindani R, *et al*. The effect of neoadjuvant therapy on esophagectomy for cT2N0M0 esophageal adenocarcinoma. Ann Surg Oncol 2024;31:228–38.
[11] Mota FC, Cecconello I, Takeda FR, *et al*. Neoadjuvant therapy or upfront surgery? A systematic review and meta-analysis of T2N0 esophageal cancer treatment options. Int J Surg 2018;54(Pt A):176–81.
[12] NCCN. NCCN Guidelines for Esophageal Cancer and Esophagogastric Junction Cancer[DB/OL]. http://www.nccn.org
[13] Mariette C, Dahan L, Mornex F, *et al*. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol 2014;32:2416–22.
[14] Stiles BM, Mirza F, Coppolino A, *et al*. Clinical T2-T3N0M0 esophageal cancer: the risk of node positive disease. Ann Thorac Surg 2011;92:491–8.
[15] Semenkovich TR, Panni RZ, Hudson JL, *et al*. Comparative effectiveness of upfront esophagectomy versus induction chemoradiation in clinical stage T2N0 esophageal cancer: a decision analysis. J Thorac Cardiovasc Surg 2018;155:2221–230.e1.
[16] Bekkar S, Gronnier C, Renaud F, *et al*. Multicentre study of neoadjuvant chemotherapy for stage I and II oesophageal cancer. Br J Surg 2016;103:855–62.
[17] Mathew G, Agha R. for the STROCSS Group. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.
[18] Guan CT, Song GH, Li BY, *et al*. Endoscopy screening effect on stage distributions of esophageal cancer: a cluster randomized cohort study in China. Cancer Sci 2018;109:1995–2002.
[19] Sivanathan V, Utz C, Thomaidis T, *et al*. Predictive value of preoperative endoscopic ultrasound (EUS) after neoadjuvant chemotherapy in locally advanced esophagogastric cancer - data from a randomized German phase II trial. Ultraschall Med 2022;43:514–21.
[20] Zuccaro G Jr, Rice TW, Vargo JJ, *et al*. Endoscopic ultrasound errors in esophageal cancer. Am J Gasteroenterol 2005;100:601–6.
[21] Rice TW, Mason DP, Murthy SC, *et al*. T2N0M0 esophageal cancer. J Thorac Cardiovasc Surg 2007;133:317–24.
[22] Mann DR, Engelhardt KE, Gibney BC, *et al*. Defining pathologic upstaging in cT1b esophageal cancer: should we consider neoadjuvant therapy? J Surg Res 2023;295:61–9.
[23] Kidane B, Korst RJ, Weksler B, *et al*. Neoadjuvant therapy vs upfront surgery for clinical T2N0 esophageal cancer: a systematic review. Ann Thorac Surg 2019;108:935–44.
[24] Crabtree TD, Kosinski AS, Puri V, *et al*. Evaluation of the reliability of clinical staging of T2N0 esophageal cancer: a review of the society of thoracic surgeons database. Ann Thorac Surg 2013;96:382–90.
[25] Speicher PJ, Ganapathi AM, Englum BR, *et al*. Induction therapy does not improve survival for clinical stage T2N0 esophageal cancer. J Thorac Oncol 2014;9:1195–201.
[26] Perez Holguin RA, Olecki EJ, Stahl KA, *et al*. Management of clinical T2N0 esophageal and gastroesophageal junction adenocarcinoma: what is the optimal treatment? J Gastrointest Surg 2022;26:2050–60.
[27] Rhodin KE, Raman V, Jawitz OK, *et al*. Patterns of use of induction therapy for T2N0 esophageal cancer. Ann Thorac Surg 2021;111:440–7.
[28] Lin HN, Chen LQ, Shang QX, *et al*. A meta-analysis on surgery with or without postoperative radiotherapy to treat squamous cell esophageal carcinoma. Int J Surg 2020;80:184–91.
[29] Yang W, Liu F, Xu R, *et al*. Is adjuvant therapy a better option for esophageal squamous cell carcinoma patients treated with esophagectomy? A prognosis prediction model based on multicenter real-world data. Ann Surg 2023; 277:e61–9.
[30] Yu S, Zhang W, Ni W, *et al*. A propensity-score matching analysis comparing long-term survival of surgery alone and postoperative treatment for patients in node positive or stage III esophageal squamous cell carcinoma after R0 esophagectomy. Radiother Oncol 2019;140:159–66.