

# Achieving adequate lymph node dissection in treating esophageal squamous cell carcinomas by radical lymphadenectomy: Beyond the scope of numbers of harvested lymph nodes

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**Abstract.** Previous studies have recommended harvesting a large number of lymph nodes (LNs) to improve the survival of patients with esophageal squamous cell carcinoma (ESCC). These studies or clinical guidelines focus on the total harvested LNs during lymphadenectomy; however, the extent of LN dissection (LND) required in patients with ESCCs remains controversial. The present study proposed a novel individualized adequate LND (ALND) strategy to compliment current guidelines to improve individualized therapeutic efficacy. For N0 cases, ALND was defined as an LN harvest of >55% of the LNs from nodal zones adjacent to the tumor location; and for N<sup>+</sup> cases, ALND was defined as 8, 8, 8, 8 or 16 LNs dissected from the involved cervical, upper, middle, lower and celiac zones, respectively. Retrospective analysis of the ESCC cohort revealed that the ALND was associated with

improved patient survival [hazard ratio (HR)=0.45 and 95% CI=0.30-0.66]. Stratified analyses revealed that the protective role of ALND was prominent, with the exception of higher pN<sup>+</sup> staged (pN2-3) cases (HR=0.52, 95% CI=0.23-1.18). Furthermore, ALND was associated with improved survival in local diseases (T1-3/N0-1; HR=0.50, 95% CI=0.30-0.84) and locally advanced diseases (T4/Nany or T1-3/N2-3; HR=0.32, 95% CI=0.15-0.68). These findings suggested that the proposed ALND strategy may effectively improve the survival of patients with ESCC.

## Introduction

Among the multimodal therapies, surgical resection of primary tumors with the involved lymph nodes (LNs) offers the best cure for patients with esophageal squamous cell carcinoma (ESCC). Although the necessity of extensive LN dissection (LND) remains debatable, the National Comprehensive Cancer Network (NCCN) guidelines (1) and the Union for International Cancer Control (UICC) staging manual (2) recommend that at least 12-15 nodes should be removed. Furthermore, subsequent to weighing the benefits and harm of radical lymphadenectomy, the 7th edition of the American Joint Committee on Cancer (AJCC) suggests resecting as many regional LNs as possible (3). Additionally, numerous studies recommend an extensive removal of 6-30 LNs for survival improvement (4-9). However, these studies and clinical guidelines focus on the extent of LND or the total number of harvested LNs (HLNs). To the best of our knowledge, no specifications have been made regarding the exact stations of the HLNs, or the number of removed nodes from the individual LN stations.

The total count of HLNs, alone, cannot provide the full information of lymphadenectomy (10,11). The association between nodal counts and survival can be modified according to the type of lymphadenectomy performed. According to previous study, the survival of patients with ESCCs undergoing en bloc resection is significantly improved when compared with those receiving transhiatal or transthoracic dissection,

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*Abbreviations:* ALND, adequate lymph node dissection; CRT, chemoradiotherapy; ESCCs, esophageal squamous cell carcinomas; HLNs, the number of harvested lymph nodes; LNs, lymph nodes; LND, lymph node dissection; LNM, lymph node metastasis; LOESS, locally weighted smoothing scatter; LNRs, lymph node ratios; OS, overall survival; PNLVI, perineural lymphatic vascular invasion; SLNM, skip lymph node metastasis; 3-FLND, 3-field lymph node dissection

*Key words:* lymphadenectomy, adequate lymph node dissection, esophageal squamous cell carcinoma, prognostic factors, multivariate analysis

even with the same threshold of 23 nodes (5). Additionally, the association between higher negative LN counts and improved prognosis was observed in patients undergoing 3-field LND (3-FLND) but not 2-FLND (12).

Therefore, it is reasonable to extend the definition of adequate LND (ALND) to optimize prognosis beyond total HLN counts. In the present study, a novel individualized ALND strategy was proposed for optimizing ESCC prognoses, which provided the number of HLNs and considered the tumor location and the metastatic status of LN zones.

## Materials and methods

**Patients.** Between January 2009 and December 2013, patients with ESCC who underwent curative esophagectomy at two independent centers (Department of Thoracic Surgery, Affiliated Zhangzhou Hospital of Fujian Medical University and Department of Thoracic Surgery, An Xi Hospital) were enrolled in the present study (Table I). All patients received preoperative computed tomography (CT) and esophagoscopy biopsy followed by pathological diagnosis. Positron emission tomography (PET) was exclusively performed on suspicious stage-IV patients. If patients met any of the exclusion criteria they were excluded from the present study. The following exclusion criteria were used: i) The patient had non-squamous cell carcinoma; ii) the patient had undergone pre-operative chemotherapy or radiotherapy; iii) the patient presented with distant metastasis; iv) the patient had a postoperative survival time of <30 days; v) the patient had non-primary esophageal carcinoma; and vi) the patient had <6 HLNs. According to the 6th UICC recommendation (13), a minimum number of 6 LNs need to be resected in order to ensure accurate pN staging. Patients who survive <30 days are likely to succumb to surgical complications, which does not agree with the purpose of the present study. Therefore, individuals whose survival time was <30 days were excluded. A total of 350 consecutive patients with ESCC were included in the cohort of the present study, 260 from Zhang Zhou Hospital (14) and 90 from An Xi Hospital.

Baseline demographic information regarding the patients with ESCC was collected on admission. The clinical and pathological traits were recorded during hospitalization, and postoperative radiotherapy and/or chemotherapy was also documented. All pathological diagnoses made prior to 2010, including tumor location, primary tumor (T stage), regional LNs (N stage), histological grade (G stage) and TNM, were revised according to the 7th edition of the AJCC Cancer Staging System (15).

**Follow-up.** All patients were followed-up every 3 months in the first 2 postoperative years and every 6 months thereafter. The last follow-up was conducted in May 2016. Information regarding patient mortality was confirmed by contacting the patient's family or retrieving the information from the local mortality registration department. The date of death or the last successful contact was recorded as the last follow-up date. Patients who were still alive at the last follow-up or with whom contact had been lost were coded as censored. Overall survival (OS) of the patients was defined as the time interval between the date of surgery and the date of the last follow-up.

**Local and distal LN zones.** In order to alleviate the impacts from different staging system, all lymph nodes documented with the Japan Esophageal Society LN codes were transformed into the 7th AJCC LN stations according to a report by Niwa *et al* (16) (Fig. 1A). Briefly, the supraclavicular and other deep cervical LNs were grouped as the cervical LN zone; the left or right upper paratracheal, anterior mediastinal, posterior mediastinal, left or right lower paratracheal along with aorticopulmonary LNs were categorized as the upper LN zone; the subcarinal, left or right tracheobronchial and middle paraesophageal LNs were classified as the middle LN zone; the lower paraesophageal, pulmonary ligament and diaphragmatic LNs belonged to the lower LN zone; and LNs located in celiac regions (paracardial, left gastric, common hepatic, splenic and celiac LNs) were grouped as the celiac LN zone. All LN zones anatomically situated nearer to or across the center of the tumor location were grouped as local LN zones, whereas distant LNs were referred to as the distal LN zones (Fig. 1B). Skip LN metastases (SLNM) were defined as the metastatic LN station situated in the distal LN zones with the local LN zones free of tumor infiltration.

**CT scanning.** CT scans were performed using a LightSpeed scanner (GE Healthcare). All patients were in the supine position and the scan images were obtained from the level of the lower neck to upper abdomen according to the following scanning protocols: 64x0.625 mm<sup>2</sup> collimation, 0.984 pitch, 5 mm slice width, 1.25-2.5 mm reconstruction increment, 1.25-2.5 mm slice spacing, 60-100 ml injection of intravenous contrast medium at a rate of 2.0-3.0 ml/s at 12 kV and 50-600 mA.

**Surgical and lymphadenectomy procedure.** The tri-incisional cervico-thoraco-abdominal procedure (McKeown type) has been adopted as a standard surgical approach (17). In the thoracic stage, esophagectomy and mediastinal lymphadenectomy (including the LNs located in the upper, middle and lower thoracic zones; Fig. 1A) were conducted via right-sided posterolateral thoracotomy. In the abdominal stage, midline laparotomy was conducted and followed by stomach mobilization, gastric tube creation and celiac node resection (station 16-20; Fig. 1A). In the cervical stage, the gastric tube was pulled up to the neck through the retrosternal or posterior mediastinal route. Subsequently, anastomosis of the alimentary tract was performed via left-sided cervicotomy. Cervical LND was not systematically undertaken for all patients. Cervical LND was adopted for patients who met the following criteria: i) The short radius of cervical LNs from the CT scan was >1 cm; or ii) the ratio of the short to long radius was <0.8. Patients receiving cervico-thoraco-abdominal LND were recorded as 3-FLND, and 2-FLND referred to thoracoabdominal node resection. The LNs located in the upper, middle, lower and celiac zones were dissected systematically (Fig. 1A).

**Statistical analysis.** Sample size needed for the Cox proportional hazard regression model was calculated according to the formula proposed by Hsieh *et al* (18). The estimated hazard ratio (HR) for ALND was 0.75, the overall event rate in the present study was 0.449, and the statistical power was set at

Table I. Associations of demographic, clinical and pathological characteristics with LND.

Characteristics	Total (n=350)		HLNs	P-value
	n	%	M (P <sub>25</sub> , P <sub>75</sub> )	
Age (years)			0.002 <sup>a</sup>	0.967 <sup>b</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	60 (53, 67)			
Sex				0.109 <sup>c</sup>
Male	259	74.0	30 (20, 43)	
Female	91	26.0	29 (18, 38)	
Tumor location				0.223 <sup>d</sup>
CE/UTE	48	13.7	24 (15, 39)	
MTE	223	63.7	30 (20, 42)	
LTE	79	22.6	30 (21, 41)	
Tumor length (cm)			0.067 <sup>a</sup>	0.220 <sup>b</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	4.0 (3.0, 4.5)			
Primary tumor				0.343 <sup>d</sup>
pT1	42	12.0	26 (15, 45)	
pT2	64	18.3	29 (18, 39)	
pT3	215	61.4	30 (21, 42)	
pT4	29	8.3	33 (24, 38)	
Regional lymph nodes				0.003 <sup>d</sup>
pN0	174	49.7	27 (17, 39)	
pN1	84	24.0	32 (24, 42)	
pN2	68	19.4	31 (23, 41)	
pN3	24	6.9	39 (28, 47)	
Histologic grade*				0.003 <sup>d</sup>
pG1	139	41.5	27 (17, 37)	
pG2	175	52.2	33 (23, 42)	
pG3	21	6.3	35 (26, 44)	
Tumor stage				0.006 <sup>d</sup>
0	3	0.9	15 (11, 56)	
IA	11	3.1	27 (10, 37)	
IB	41	11.7	24 (16, 39)	
IIA	63	18.0	24 (17, 35)	
IIB	70	20.0	33 (19, 44)	
IIIA	71	20.3	32 (24, 42)	
IIIB	50	14.3	29 (21, 46)	
IIIC	41	11.7	35 (27, 44)	
Skip LNM <sup>#</sup>				0.499 <sup>c</sup>
Yes	90	51.1 <sup>e</sup>	32 (24, 44)	
No	86	48.9 <sup>e</sup>	33 (25, 44)	
LVI				<0.001 <sup>c</sup>
Yes	72	20.6	36 (27, 50)	
No	278	79.4	28 (18, 39)	
PNI				<0.001 <sup>c</sup>
Yes	62	17.7	40 (30, 52)	
No	288	82.3	27 (18, 38)	
Fields of lymphadenectomy				<0.001 <sup>c</sup>
3-FLND	185	52.9	35 (26, 47)	
2-FLND	165	47.1	23 (17, 34)	

Table I. Continued.

Characteristics	Total (n=350)		HLNs	P-value
	n	%	M (P <sub>25</sub> , P <sub>75</sub> )	
Residual tumor				0.998 <sup>d</sup>
Rx	9	2.6	30 (18, 36)	
R0	337	96.3	29 (20, 41)	
R1	4	1.1	25 (24, 41)	
Positive lymph nodes			0.187 <sup>a</sup>	<0.001 <sup>b</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	1 (0, 3)			

<sup>a</sup>Spearman correlation coefficients; <sup>b</sup>P-values for Spearman correlation; <sup>c</sup>P-values for two independent samples Mann-Whitney U tests; <sup>d</sup>P-values for independent samples Kruskal-Wallis H tests; <sup>e</sup>The proportion of skip lymph node metastases was calculated for the pN1-3 cases. 2-FLND, two-field lymph node dissection; 3-FLND, three-field lymph node dissection; CE, cervical esophagus; HLN, harvested LNs number; LTE, lower thoracic esophagus; LVI, lymphovascular invasion; MTE, middle thoracic esophagus; PNI, perineural invasion; UTE, upper thoracic esophagus. <sup>f</sup>The information of histologic grade was not available for 15 patients. <sup>g</sup>Skip LNM was defined only for the patients who had metastatic LNs, therefore N0 cases were excluded.

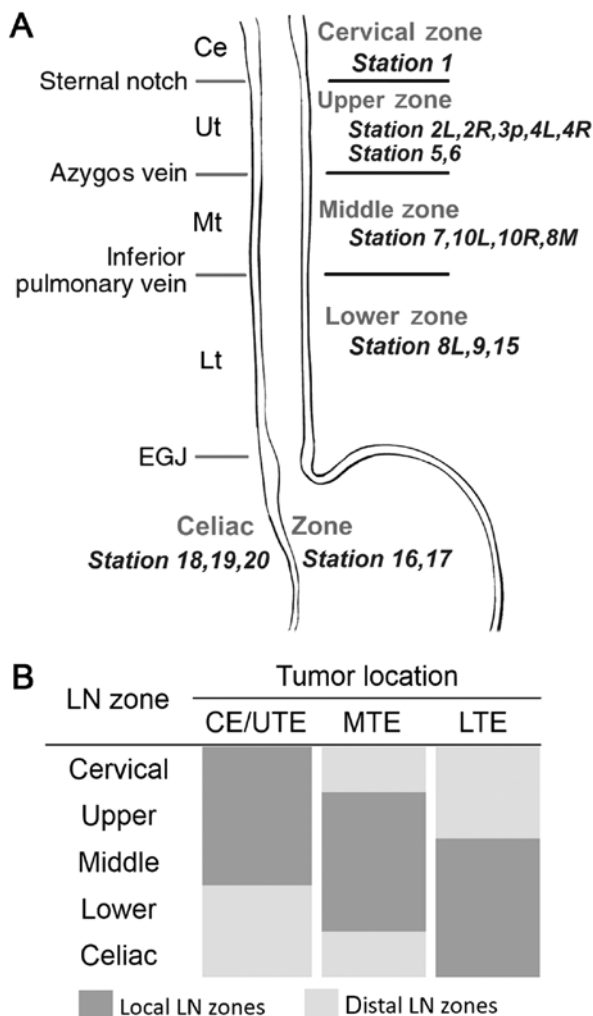


Figure 1. LN zones of esophageal squamous cell carcinoma. (A) American Joint Committee on Cancer LN stations were regrouped as LN zones according to their locations. (B) Local LN zones were defined as the LN zones situated anatomically nearer to the center of the tumor location. Ce, cervical; CE/UTE, cervical or upper thoracic esophagus; EGJ, esophagogastric junction; Lt, lower thoracic; LTE, lower thoracic esophagus; LN, lymph node; Mt, middle thoracic; MTE, middle thoracic esophagus; Ut, upper thoracic.

0.80 with a type I error rate of 0.05. The required total sample size could be approximated at 330.

Due to the deviated distribution of the HLNs, median, 25th and 75th percentiles were adopted in the present study. Mann-Whitney U tests or Kruskal-Wallis H tests were used to compare the median number of HLNs in the categorical groups. The Benjamini-Hochberg corrections were applied for repeated comparisons between two independent groups. The post hoc Bonferroni corrections were used for examining pair-wise differences following Kruskal-Wallis tests. Spearman correlation coefficients ( $r_s$ ) were applied to evaluate the association between HLNs and continuous variables, including age, tumor length and number of positive LNs (PLNs).

The survival of patients with ESCC was calculated using the Kaplan-Meier method. HLNs were divided into four categories according to quartiles (<20, 20-29, 30-40 and >40). The association between quartered HLNs and OS was evaluated using the log-rank test. The percentage of total HLNs in local zones was calculated by dividing the number of HLNs in the local zones by the total number of HLNs. In order to determine the optimal cut-points of local HLN percentages for maximum OS difference, the X-tile algorithm was used (19). For N<sup>+</sup> cases, LN ratios (LNRs) were computed as the ratio of PLNs to HLNs. Locally weighted smoothing scatter plot (LOESS) curves were plotted to identify the thresholds of HLNs at the inflection points on the curves.

Prior to Cox regression analysis, the variables were investigated for collinearity, and the variance inflation factor threshold was set at 3. The proportional hazards assumption was assessed using Schoenfeld residuals (20). Multivariate Cox regression analysis was performed to verify the therapeutic values of ALND while the other confounders were controlled, including sex, age, tumor location, tumor length, regional LNs (N stage), depth of tumor invasion (T stage), histological grade (G stage), perineural lymphatic vascular invasion (PNLVI), chemoradiotherapy (CRT) and medical centers. The HR and the corresponding 95% CI were used to express the protective effect of ALND. Furthermore, stratified analyses were

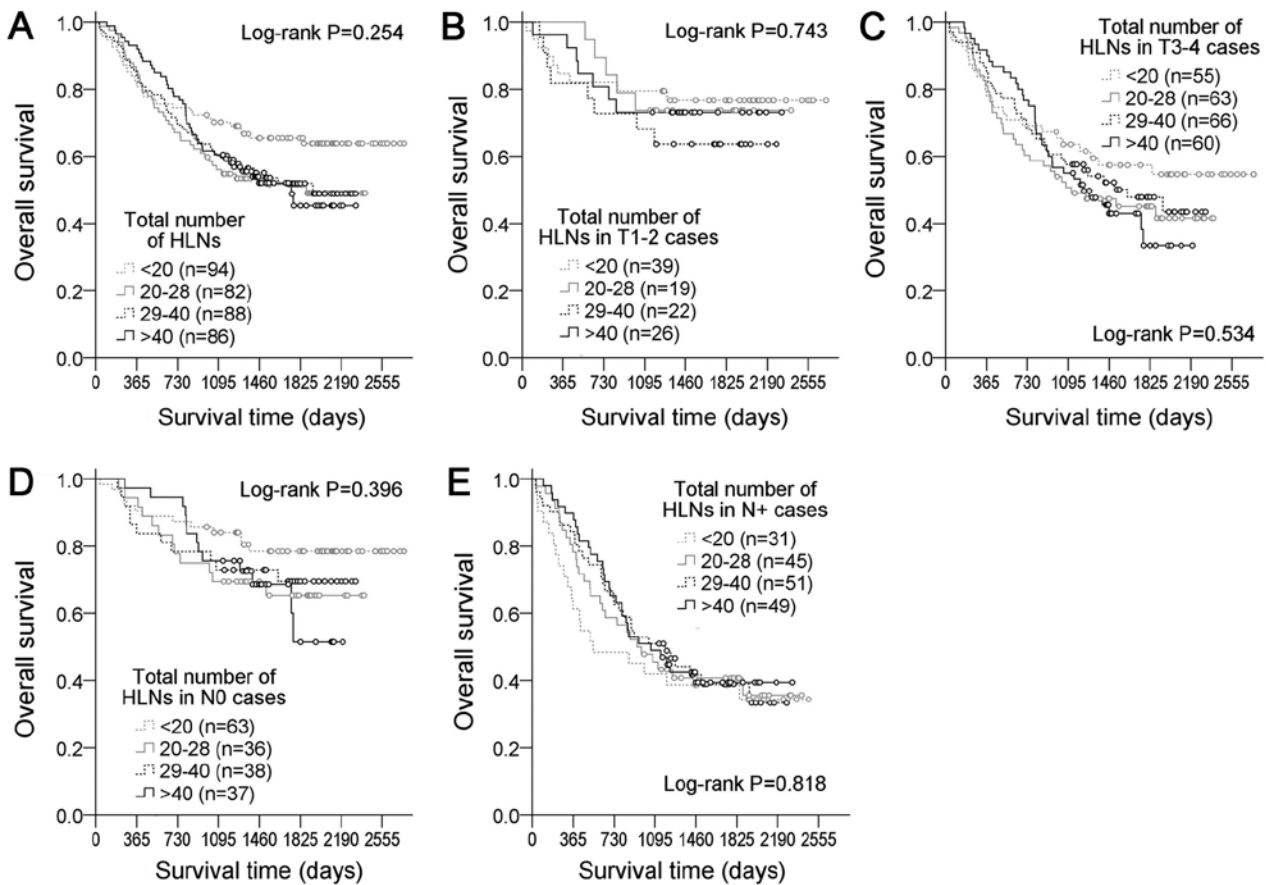


Figure 2. There is no association between the total number of HLNs and overall survival in patients with ESCC. (A) Higher HLN count was not identified to be associated with improved survival (log-rank,  $P=0.254$ ). No association was identified in the strata of (B) T1-2 (log-rank,  $P=0.743$ ), (C) T3-4 (log-rank,  $P=0.534$ ), (D) N0 (log-rank,  $P=0.396$ ) and (E)  $N^+$  cases (log-rank,  $P=0.818$ ). HLNs, harvested lymph nodes; ESCC, esophageal squamous cell carcinoma.

performed for well-established prognostic factors, including PNLVI, T stage, N stage, G stage, TNM, CRT, fields of LND and SLNM, to verify the prognostic significance of ALND within each stratum.

The statistical analyses were conducted using SPSS version 19.0 (IBM Corp.). All statistical tests performed were two-tailed.  $P<0.05$  was considered to indicate a statistically significant difference.

## Results

**Lymphadenectomy of 350 patients with ESCC.** Details of demographic, clinical and pathological characteristics are summarized in Table I. The median value of HLNs was 29, with the lower and upper quartile at 20 and 41. The total number of HLNs was correlated with the count of PLNs ( $r_s=0.187$ ,  $P<0.001$ ). Patients undergoing 3-FLND had significantly more LNs resected when compared with those receiving 2-FLND ( $P<0.001$ ). Factors such as lymphovascular invasion, perineural invasion, pG, pN and TNM classification were associated with HLNs ( $P<0.05$ ; Table I, Supplementary Table I).

**There is no association between the total number of HLNs and OS in patients with ESCC.** The median follow-up duration was 1321 days. The 5-year OS rate of patients with ESCC was 54% (95% CI, 49-60%). A higher count of HLNs was

not identified to be associated with improved OS ( $P=0.254$ ; Fig. 2A). Furthermore, stratified analyses based on T stage (Fig. 2B and C) and N stage (Fig. 2D and E) also yielded non-significant results ( $P=0.743$ ,  $P=0.534$ ,  $P=0.396$  and  $P=0.818$  for T1-2, T3-4, N0 and  $N^+$  cases, respectively).

**Selective lymphadenectomy based on tumor locations is associated with improved survival of N0 patients.** For all cases, more LNs were harvested in the local zones compared with the distal zones, regardless of tumor location and metastatic status ( $P<0.05$ ; Fig. 3A and B). These findings suggested a surgical preference to dissect LNs in regions near the tumor location rather than far from it. The optimal cut-off point for the percentages of HLNs in the local LN zones to maximize survival differences in N0 patients was set at 55% using the X-tile algorithm ( $P=0.011$ ; Fig. 3C). However, no association was observed in  $N^+$  patients ( $P=0.846$ ; Fig. 3D).

**Thresholds of HLNs from the metastatic LN zones in  $N^+$  patients.** For  $N^+$  patients, surgeons preferred to dissect more LNs in the specific LN zone when metastasis was evident ( $P<0.05$ ; Table II) For example, when the cervical LN zones were involved, surgeons would resect more LNs in the cervical zone compared with in the uninvolved area in the same zone ( $P<0.001$ ; Table II). A similar dissection preference was also observed in other LN zones ( $P<0.05$ ; Table II), except for the nodes in celiac zones.

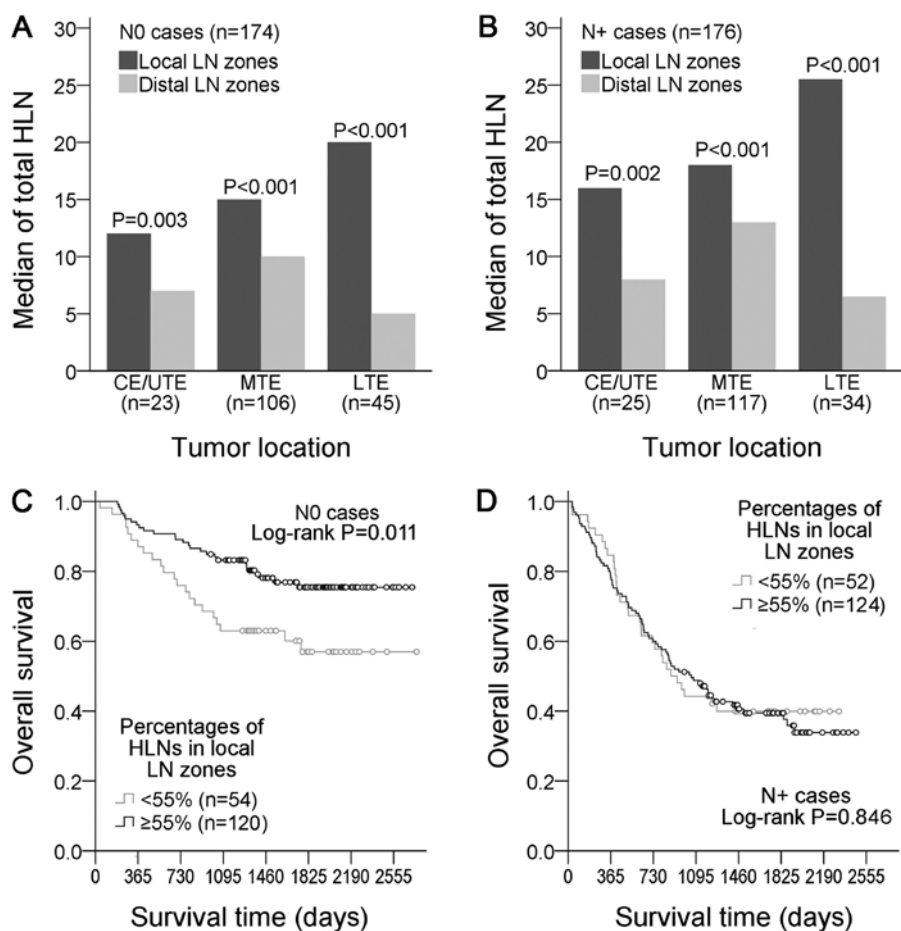


Figure 3. There is an association between higher percentages of HLNs in the local LN zones and improved survival in the N0 patients but not in N+ patients. (A) More LNs were dissected from the local LN zones compared with those from distal zones in all CE/UTE, MTE and LTE for patients of N0 status. (B) More LNs were dissected from the local LN zones compared with those from distal zones in all CE/UTE, MTE and LTE for patients of N+ status. (C) The optimal cut-off point for the percentage of the local HLNs, which maximized the survival difference in the N0 cases, was set at 55%. A high percentage of HLNs in the local LN zones was associated with improved survival in the N0 cases (log-rank  $P=0.011$ ). (D) A cut-point of 55% HLNs in the local LN zones was not associated with improved survival in the N+ cases (log-rank  $P=0.846$ ). LN, lymph node; HLNs, harvested lymph nodes.

Scatter plots were applied to depict the association between the HLNs and LNRs in N+ patients. By identifying the inflection points on the LOESS curves, the thresholds for ALND were set at 8, 8, 8, 8 and 16 for cases with cervical, upper, middle, lower and celiac metastases, respectively (Fig. 4A-E). Metastatic patients who received ALND exhibited improved survival compared with those who did not ( $P=0.009$ ; Fig. 4F).

**Definition of ALND beyond HLNs.** According to the aforementioned analyses, ALND was designated as an LND strategy that considered tumor location and metastatic nodal zones (Fig. 5). For N0 patients, ALND was defined as a resection of  $>55\%$  of the LNs distributed in the LN zones adjacent to the tumor location (local LN zones). For N+ patients, ALND was defined as a sufficient LN resection from the involved LN zones. For instance, for N+ patients with metastases in the cervical and celiac zones, ALND could be achieved by resecting at least 8 and 16 nodes in the two zones, respectively. Other uninvolved nodal zones were subjected to standard lymphadenectomy.

For N0 patients, those who received ALND did not yield more LNs compared with those who did not receive ALND ( $P=0.302$ ; Fig. 6A). Furthermore, the percentages of HLNs

in the local LN zones were not correlated with the total number of HLNs, regardless of whether they received ALND ( $r_s=-0.16$ ,  $P=0.180$ ; Fig. 6B) or not ( $r_s=0.16$ ,  $P=0.258$ ; Fig. 6B). However, N+ patients that underwent ALND yielded more LNs compared with those without ALND ( $P<0.001$ ; Fig. 6A). A higher count of HLNs in the ALND group was primarily due to more aggressive resection in the metastatic nodal zones, but not in the uninvolved zones ( $P<0.05$ ; Fig. 6C). For example, when lymph node metastasis (LNM) was detected in the celiac zone, in order to achieve ALND, surgeons would resect more LNs in the abdomen only ( $P<0.001$ ; Fig. 6C).

**ALND is associated with improved survival in patients with ESCC.** Since several factors were associated with ALND (tumor location, pT stage, pN stage, fields of LND and CRT, all  $P<0.05$ ; Table III), stratified Cox regressions were performed with these factors and other well-established prognostic factors, such as PNLVI, pG and the presence of SLNMs. The therapeutic values of ALND were confirmed for all cases with the exception of pT1-2 cases (HR=0.42, 95% CI=0.15-1.18,  $P=0.100$ , Model 3; Table IV). When using the whole cohort (Model 15; Table IV), ALND was associated with improved survival (HR=0.45, 95% CI=0.30-0.66,  $P<0.001$ ). For cases

Table II. Association of HLNs in specific LN zones with metastases status for N<sup>+</sup> patients (n=176).

LN zones metastases status	HLNs in specific LN zones				
	Cervical	Upper	Middle	Lower	Celiac
	M (P <sub>25</sub> ,P <sub>75</sub> )	M (P <sub>25</sub> ,P <sub>75</sub> )	M (P <sub>25</sub> ,P <sub>75</sub> )	M (P <sub>25</sub> ,P <sub>75</sub> )	M (P <sub>25</sub> ,P <sub>75</sub> )
<b>Cervical</b>					
No (n=135)	0 (0, 2)	7 (4, 11)	8 (4, 11)	2 (1, 4)	12 (6, 18)
Yes (n=41)	3 (2, 7)	6 (4, 13)	7 (4, 12)	2 (1, 5)	12 (5, 17)
P-value <sup>a</sup>	<0.001	0.969	0.986	0.986	0.957
<b>Upper</b>					
No (n=97)	1 (0, 3)	5 (2, 11)	8 (4, 12)	2 (1, 5)	13 (8, 18)
Yes (n=79)	1 (0, 2)	9 (5, 12)	7 (4, 11)	2 (1, 4)	11 (5, 15)
P-value <sup>a</sup>	0.478	0.009	0.784	0.851	0.131
<b>Middle</b>					
No (n=108)	1 (0, 3)	6 (3, 11)	7 (4, 11)	2 (1, 5)	12 (7, 18)
Yes (n=68)	1 (0, 2)	8 (4, 11)	9 (5, 13)	2 (1, 4)	12 (6, 17)
P-value <sup>a</sup>	0.784	0.478	0.030	0.851	0.784
<b>Lower</b>					
No (n=126)	1 (0, 2)	7 (4, 11)	8 (4, 12)	2 (0, 3)	12 (6, 17)
Yes (n=50)	1 (0, 3)	7 (2, 12)	8 (4, 11)	4 (3, 7)	13 (6, 16)
P-value <sup>a</sup>	0.986	0.969	0.862	<0.001	0.969
<b>Celiac</b>					
No (n=92)	1 (0, 3)	7 (4, 12)	8 (4, 12)	2 (1, 4)	10 (4, 17)
Yes (n=84)	1 (0, 2)	6 (3, 11)	7 (4, 11)	2 (1, 5)	12 (8, 18)
P-value <sup>a</sup>	0.280	0.243	0.604	0.933	0.243

<sup>a</sup>Independent samples Mann-Whitney U tests with Benjamini-Hochberg correction were performed to examine the differences in median values of HLNs. HLN, harvested lymph node; LN, lymph node; M, median.

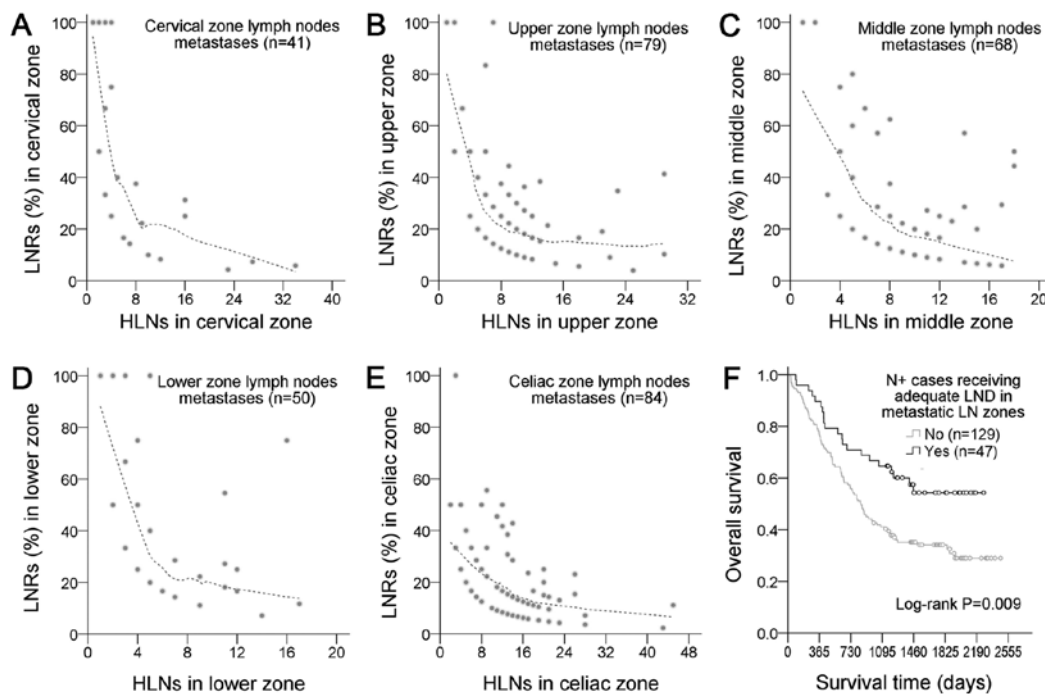


Figure 4. Thresholds for defining ALND in N<sup>+</sup> patients. Thresholds for ALND were identified as the inflection points on LOESS curves to identify the corresponding values on the horizontal axis, which indicated that the HLNs were (A) 8, (B) 8, (C) 8, (D) 8 and (E) 16 for cases with cervical, upper, middle, lower and celiac zone metastases, respectively. (F) Improved overall survival was observed in N<sup>+</sup> patients who received ALND (log-rank, P=0.009). ALND, adequate lymph node dissection; HLN, harvested lymph node; LNR, lymph node ratio; LOESS, locally weighted smoothing scatter.

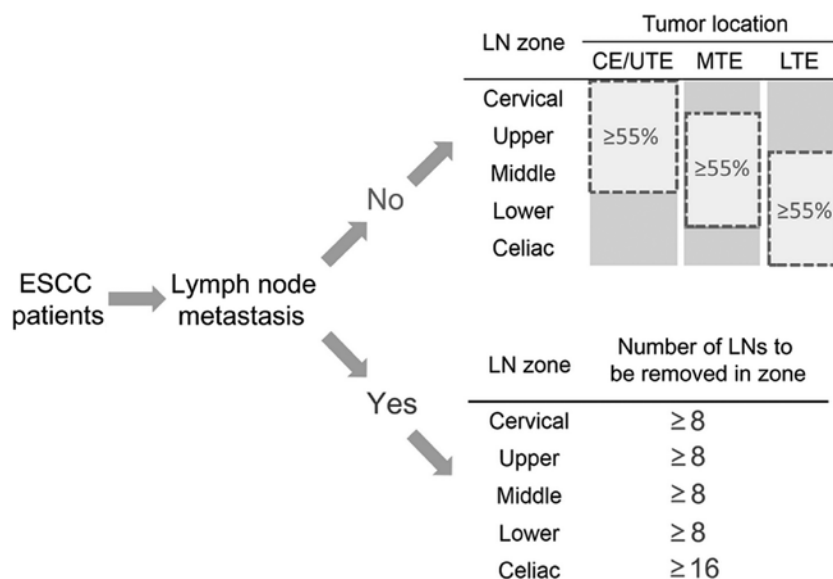


Figure 5. Definition of ALND in ESCC treated with radical lymphadenectomy. For the N0 cases, ALND was defined as a LN count of  $\geq 55\%$  of the resected LNs distributed in the local LN zones. For the N+ cases, a sufficient number of HLNs needed to be resected from the involved LN zones. ALND, adequate lymph node dissection; CE/UTE, cervical or upper thoracic esophagus; ESCC, esophageal squamous cell carcinoma; HLNs, harvested lymph nodes; LN, lymph node; LTE, lower thoracic esophagus; MTE, middle thoracic esophagus.

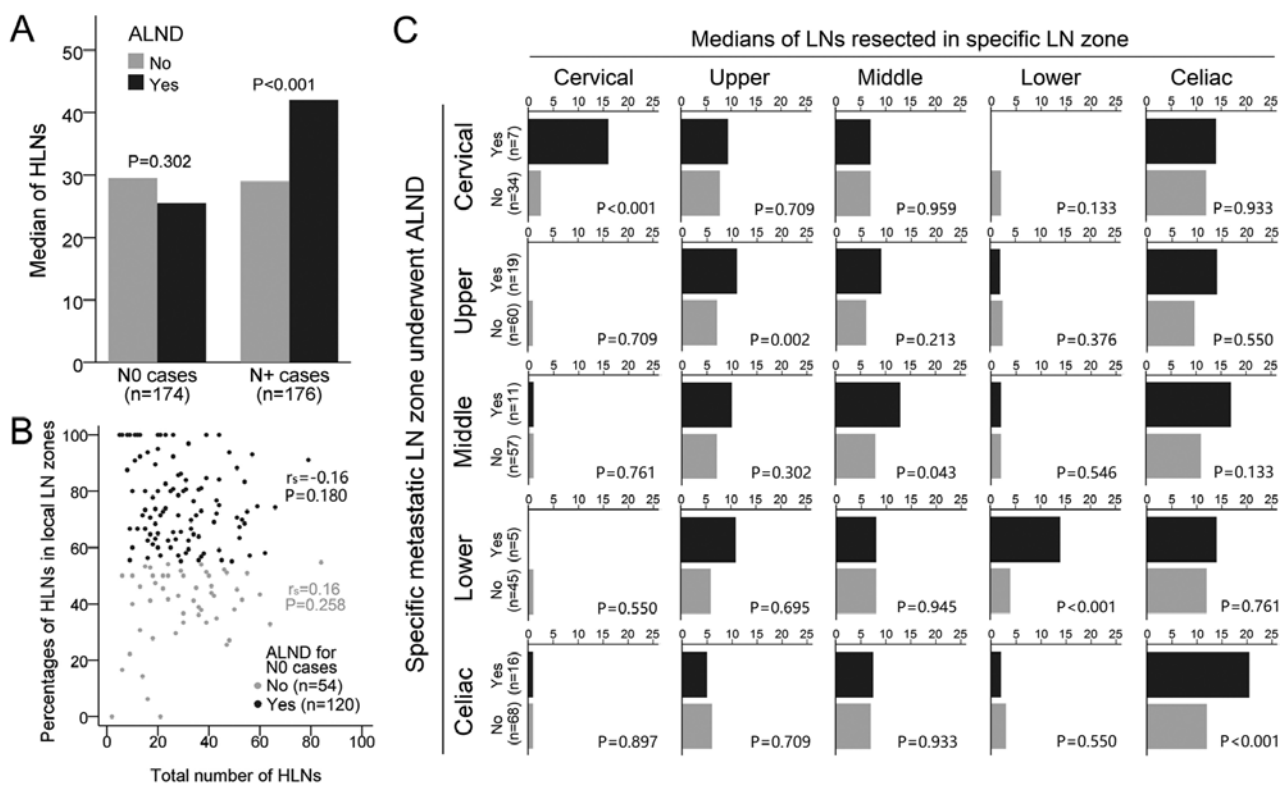


Figure 6. There is no association between the classification of ALND and the total number of HLNs. (A) Median numbers of HLNs in the N0 or N+ cases were compared between cases treated with or without ALND. (B) Correlations of the percentages of LNs resected from the local LN zones with the total number of HLNs in the N0 cases were demonstrated. (C) Median numbers of HLNs in different nodal zones were compared between N+ cases treated with or without ALND. All P-values were corrected using the Benjamini-Hochberg method. ALND, adequate lymph node dissection; HLNs, harvested lymph nodes; LN, lymph node.

with  $\geq 15$  HLNs (adequately staged ESCCs), ALND was associated with improved survival in N0 (HR=0.45, 95% CI=0.20-0.97,  $P=0.043$ ) and N+ patients (HR=0.41, 95% CI=0.22-0.75,  $P=0.004$ ; Table V).

Furthermore, the protective role of ALND was examined in several relatively homogeneous subgroups. No significant associations between ALND and survival rate were found for subgroups of pN1 (HR=0.44, 95% CI=0.19-1.01,  $P=0.170$ ;



Table III. Associations of demographic, clinical and pathological characteristics with ALND.

Characteristics	ALND				P-value
	No (n=183)		Yes (n=167)		
	n	%	n	%	
Age (years)					0.549 <sup>a</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	60 (53, 67)		59 (53, 66)		
Sex					0.729 <sup>b</sup>
Male	134	73.2	125	74.9	
Female	49	26.8	42	25.1	
Tumor location					<0.001 <sup>b</sup>
CE/UTE	24	13.1	24	14.4	
MTE	134	73.2	89	53.3	
LTE	25	13.7	54	32.3	
Tumor length (cm)					0.295 <sup>a</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	4.0 (3.0, 5.0)		4.0 (3.0, 5.0)		
pT					0.015 <sup>b</sup>
pT1	22	12.0	20	12.0	
pT2	22	12.0	42	25.1	
pT3	122	66.7	93	55.7	
pT4	17	9.3	12	7.2	
pN					<0.001 <sup>b</sup>
pN0	54	29.5	120	71.8	
pN1	55	30.1	29	17.4	
pN2	52	28.4	16	9.6	
pN3	22	12.0	2	1.2	
pG*					0.216 <sup>b</sup>
pG1	68	37.8	71	45.8	
pG2	98	54.4	77	49.7	
pG3	14	7.8	7	4.5	
Skip LNM <sup>#</sup>					0.176 <sup>b,c</sup>
No	67	51.9	19	40.4	
Yes	62	48.1	28	59.6	
PNLVI					0.133 <sup>b</sup>
No	126	68.9	127	76.0	
Yes	57	31.1	40	24.0	
Fields of LND					0.047 <sup>b</sup>
3-FLND	77	42.1	88	52.7	
2-FLND	106	57.9	79	47.3	
CRT					0.012 <sup>b</sup>
No	84	45.9	99	59.3	
Yes	99	54.1	68	40.7	
HLNs					0.835 <sup>a</sup>
Median (P <sub>25</sub> , P <sub>75</sub> )	29 (21, 40)		29 (19, 44)		

<sup>a</sup>P-values for 2 independent samples Mann-Whitney U tests; <sup>b</sup>P-values for Pearson's  $\chi^2$  tests; <sup>c</sup>The comparison was performed in the N<sup>+</sup> cases. 2-FLND, two-field lymph node dissection; 3-FLND, three-field lymph node dissection; ALND, adequate lymph node dissection; CE, cervical esophagus; CRT, chemoradiotherapy; HLN, harvested lymph node; LNM, lymph node metastasis; LTE, lower thoracic esophagus; MTE, middle thoracic esophagus; PNLVI, perineural lymphatic vascular invasion; UTE, upper thoracic esophagus. \*The histologic grade information was not available for 3 cases in the non-ALND group and 12 cases in the ALND group. <sup>#</sup>Skip LNM was defined only for the patients who had metastatic LNs, therefore N0 cases were excluded.

Table IV. Stratified analysis of the therapeutic benefits of ALND.

Model <sup>a</sup>	Stratified factors	ALND		
		Hazard ratio <sup>b</sup>	(95% CI)	P-value
PNLVI				
1	No (n=253)	0.52	(0.31, 0.88)	0.014
2	Yes (n=97)	0.26	(0.13, 0.52)	<0.001
Primary tumor				
3	pT1-2 (n=106)	0.42	(0.15, 1.18)	0.100
4	pT3-4 (n=244)	0.44	(0.28, 0.68)	<0.001
Regional lymph nodes				
5	pN0 (n=174)	0.45	(0.22, 0.92)	0.029
6	pN <sup>+</sup> (n=176)	0.47	(0.26, 0.82)	0.008
Histological grade				
7	pG1 (n=139)	0.45	(0.25, 0.78)	0.005
8	pG2-3 (n=196)	0.38	(0.21, 0.68)	0.001
CRT				
9	No (n=183)	0.37	(0.21, 0.65)	0.001
10	Yes (n=167)	0.56	(0.32, 0.99)	0.047
Fields of LND				
11	2-FLND (n=165)	0.41	(0.22, 0.74)	0.004
12	3-FLND (n=185)	0.47	(0.27, 0.82)	0.007
Skip LNM (for N+ cases)				
13	No (n=86)	0.41	(0.17, 1.00)	0.049
14	Yes (n=90)	0.44	(0.20, 0.99)	0.046
All cases				
15	Combined (n=350)	0.45	(0.30, 0.66)	<0.001

<sup>a</sup>Fields of LND and total number of HLN did not meet the proportional hazard assumption, and therefore were excluded from the following 15 models. <sup>b</sup>The hazard ratios of ALND were adjusted for sex (male, female), age (continuous), tumor location (CE/UTE, MTE and LTE), tumor length (continuous), pN (N0, N1 and N2-3), pT (T1, T2, T3 and T4), pG (G1, G2-3), PNLVI (yes, no), CRT (yes, no) and medical centers (Center 1, Center 2). 2-FLND, two-field lymph node dissection; 3-FLND, three-field lymph node dissection; ALND, adequate lymph node dissection; CE, cervical esophagus; CRT, chemoradiotherapy; HLN, harvested lymph node; LNM, lymph node metastasis; LTE, lower thoracic esophagus; MTE, middle thoracic esophagus; PNLVI, perineural lymphatic vascular invasion; UTE, upper thoracic esophagus.

Table V. Association between ALND and prognoses in adequately staged patients with ESCC stratified by nodal status<sup>a</sup>.

pN	ALND		Hazard ratio <sup>b</sup>	(95% CI)	P-value
	no (n, %)	yes (n, %)			
N0	45, 30.8	101, 69.2	0.45	(0.20, 0.97)	0.043
N <sup>+</sup>	118, 72.4	45, 27.6	0.41	(0.22, 0.75)	0.004

<sup>a</sup>Adequately staged ESCCs were defined as patients with harvested lymph nodes  $\geq 15$  (Union for International Cancer Control recommendation) (2). <sup>b</sup>The hazard ratios of ALND were adjusted for sex (male, female), age (continuous), tumor location (cervical and upper thoracic esophagus, middle thoracic esophagus and lower thoracic esophagus), tumor length (continuous), number of positive nodes (continuous), pT (T1, T2, T3 and T4), pG (G1, G2-3), perineural lymphatic vascular invasion (yes, no), chemoradiotherapy (yes, no) and medical centers (Center 1, Center 2). ALND, adequate lymph node dissection; ESCC, esophageal squamous cell carcinoma.

Fig. 7A), pN2 (HR=0.45, 95% CI=0.18-1.10, P=0.157; Fig. 7B) and pN2-3 (HR=0.52, 95% CI=0.23-1.18, P=0.069; Fig. 7D). However, trends toward improved survival with ALND were observed pN1-2 (HR=0.49, 95% CI=0.28-0.88, P=0.033; Fig. 7C). Additionally, ALND was associated with improved survival in local diseases (T1-3/N0-1; HR=0.50, 95% CI=0.30-0.84,

P<0.001; Fig. 7E) and locally advanced diseases (T4/Nany or T1-3/N2-3; HR=0.32, 95% CI=0.15-0.68, P=0.022; Fig. 7F).

Finally, in order to illustrate the efficacy of the proposed ALND, the current cohort was analyzed with five other LND recommendations proposed by the NCCN (1) (Fig. 8A), UICC (2) (Fig. 8B), Rizk *et al* (6) (Fig. 8C),

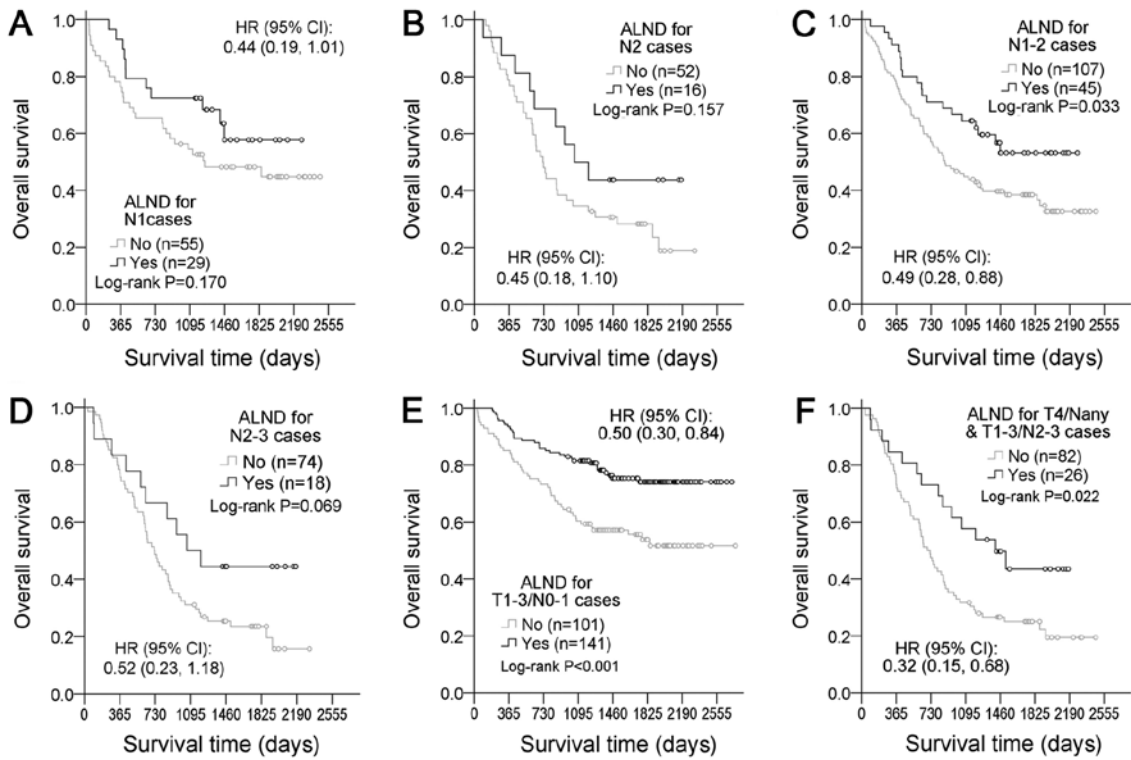


Figure 7. Therapeutic effect of ALND in the relative homogeneous subgroups of patients with esophageal squamous cell carcinoma. ALND efficacy was further evaluated in (A) pN1 cases, (B) pN2 cases, (C) pN1-2, (D) pN2-3, (E) local disease patients (T1-3/N0-1) and (F) locally advanced disease (T4/Nany and T1-3/N2-3). HRs of ALND were adjusted for sex, age, tumor length, PNLVI, number of positive LNs, pT, pG, chemoradiotherapy, tumor location and medical center. ALND, appropriate lymph node dissection; HR, hazard ratio; PNLVI, perineural lymphatic vascular invasion.

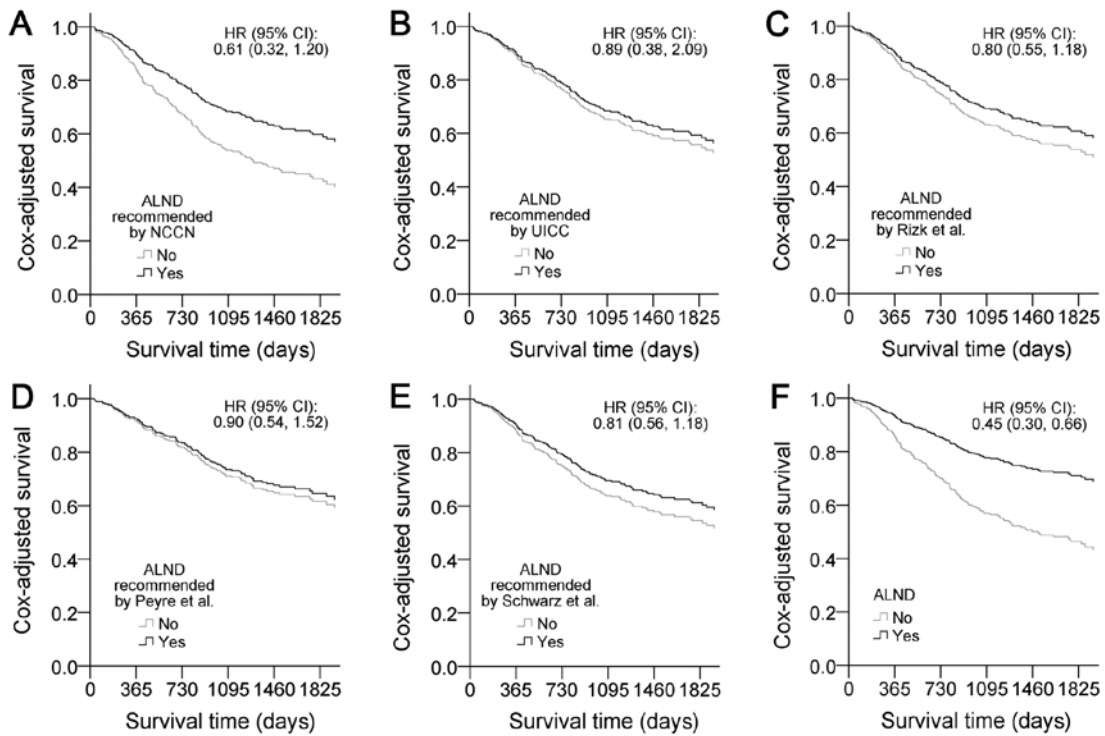


Figure 8. Comparisons of Cox-adjusted survival curves of ALND. Cox-adjusted survival curves were generated using multiple Cox regression, which included sex, age, tumor location, tumor length, pG, pN, PNLVI, chemoradiotherapy, medical centers and ALND. (A) ALND recommendation from the NCCN guidelines (1) is  $\geq 15$  HLNs. (B) At least 12 total HLNs are required for T1b-3/N0-1 cases according to the UICC (2). (C) Rizk *et al* (6) recommended optimal T stage-dependent lymphadenectomy, and set the thresholds at 10, 20 and 30 HLNs for pT1, pT2 and pT3/4 cases, respectively. (D) Peyre *et al* (5) defined ALND by the removal of  $\geq 23$  nodes. (E) Schwarz *et al* (9) recommended a resection of  $\geq 30$  LNs to achieve ALND. (F) Although the survival curves for cases receiving ALND demonstrated improved prognosis, none of the five recommendations were verified as a significant factor by Cox regression models; the ALND proposed in the present study was significant. ALND, adequate lymph node dissection; HLNs, harvested lymph nodes; LN, lymph node; NCCN, National Comprehensive Cancer Network; pG, histological grade; pN, LN metastases; PNLVI, perineural lymphatic vascular invasion; UICC, Union for International Cancer Control.

Peyre *et al* (5) (Fig. 8D) and Schwarz *et al* (9) (Fig. 8E). The results indicated that none of the recommended LNDs outperformed the proposed ALND (Fig. 8F).

## Discussion

In the present study, no significant association between the total number of HLN and OS was identified. This lack of association between more extensive LND and improved survival has also been documented by other studies, including an international multicenter study (21), a long follow-up case cohort in a high-volume center (22), nation-wide cohorts (23,24), randomized clinical trials (25-27), retrospectively analyzed cases receiving right-sided transthoracic or left-sided thoracoabdominal approaches (28), patients with early-stage ESCC (29) and patients with ESCC undergoing neoadjuvant chemotherapy (30). Additionally, evidence indicates that the survival benefits from higher HLNs or radical LND can be attributable, at least, partly to stage migration (improved staging rather than improved therapeutic benefit of the dissection itself) (31-33). Since most cases in the present study had more than 15 HLNs, which indicated that the metastatic nodes could have already been removed (2), further nodal resection may not bring additional benefits to survival.

It is well known that the depth of tumor invasion is associated with nodal metastases, which causes a nodal metastatic pattern that is predisposed to tumor location (34). Additionally, a recent study claimed that the extent of LND should be estimated by the dissected zones and modified according to the tumor location (35). In the present study, surgeons tended to harvest more nodes in the region adjacent to the tumor location (the local LN zones) in order to remove potential metastatic nodes. However, as indicated in the present study, this selective LND had a protective effect for N0 patients only.

Since the presence of abundant longitudinal lymphatic drainage in the submucosa facilitates the spread of cancer cells to distant LNs (36), SLNMs were frequently observed in the present study (51% of N<sup>+</sup> patients). Additionally, the direction of metastatic lymphatic flow from the tumor may be altered according to the depth of invasion (37), which can reduce the accuracy of predicting metastatic LN sites. Therefore, selective lymphadenectomy based on the site of primary tumors may fail to capture these skipped or unexpected metastatic nodes, which may partly explain the lack of association between the percentages of local HLNs and survival rates of N<sup>+</sup> patients.

In order to successfully remove nodes with cancerous infiltration, lymphadenectomy for the N<sup>+</sup> patients should focus on the metastatic LN zones. It has been reported that micrometastases are highly prevalent in pathologically negative nodes (38,39), and sufficient dissection may block the spreading of tumor cells. However, to the best of our knowledge, no previous study has specified the number of LNs that need to be resected in the exact site. By using LOESS curves, cut-offs of LN counts for adequately removing potentially metastatic nodes in specific zones were set. In the cohort of the present study, N<sup>+</sup> patients with sufficient LNs resected from the metastatic zones exhibited improved survival compared with those who did not receive ALND, even in the cases of patients with SLNMs.

By integrating the requirements for removing the potentially involved LNs in the N0 and N<sup>+</sup> patients, a novel definition of ALND was proposed. The total numbers of HLNs in the aforementioned strategy were not addressed out of the following considerations: i) In the present study, most cases received a radical resection, which yielded a high LN count (median HLNs value=29); and ii) no statistical association was evident between a higher LN total and improved survival in the present study.

Although non-significant results were observed in pN1 and pN2 patients, trends toward improved survival were observed for ALND in these subgroups. Additionally, following the merging of pN1 and pN2 subgroups, significantly improved survival was indicated, which suggested the protective role of ALND. However, the present study failed to verify the protective outcome in pN2-3 cases. Therefore, ALND may have limited effects on cases with high pN stages. The results were consistent with the current opinions that radical surgery has limited value for cases with systemic nodal spread diseases (40,41).

Two or three-field lymphadenectomy could produce different postoperative lymph node distributions, which can influence the chances of ALND and survival. Therefore, in the present study, the protective role of ALND within each stratum was evaluated. The results revealed significant associations between ALND and improved survival in the two strata. Therefore, it was likely that the association between ALND and prognosis was not modified by the fields of lymphadenectomy.

In order to determine the efficacy of the proposed ALND, the current cohort was examined using five other recommended guidelines. The findings indicated that none of the recommended guidelines outperformed the proposed ALND. The difference in efficacy may be due to two reasons. Firstly, the multicenter populations included in studies by Rizk *et al* (6), Peyer *et al* (5) and Schwarz *et al* (9) were primarily composed of patients with adenocarcinoma (57-60%), which has been reported to have a different lymphatic spread pattern from that of squamous cell carcinoma (42). Secondly, all three studies reported few HLNs during lymphadenectomy, with the median LN counts ranging between 8 and 17, which indicates that the observed survival benefits from an extensive LND were likely to be confounded by inadequate staging (31,32). Therefore, the ALND proposed in the present study was more applicable to patients with ESCC receiving radical lymphadenectomy.

Although ALND in neoadjuvant chemotherapy (nCT) patients could not be evaluated in the present study, the impact of nCT on lymphadenectomy has been reported elsewhere. The nCT may affect the preoperative LND strategy and the preferences/habits of nodal dissection during surgery, but not the therapeutic value of LND (30,43). In our clinical centers, a small number of ESCC cases (<13%) received nCT and were not included in the present study. Investigations into the effect of nCT on ALND will be conducted in the future when a sufficient sample pool is available.

There are several limitations of the present study. Although the proportion of pN3 patients in the present study (6.9%) was similar to that of a previous large-scale study (6.1%) (44), which consisted of 1195 patients with ESCC treated with surgery alone, the sample size of pN3 in the present study was small (n=28). Furthermore, 52.9% of patients were treated with 3-FLND and the rest of the patients were treated with extended

2-FLND, which indicates a different dissection preference from what is predominantly practiced in Europe and North America, where the standard is 2-FLND (45). This dissection preference limits the application of ALND when the cervical LN zone is involved. In addition, as it is difficult to predict specific nodal metastases even with PET-CT and endoscopic ultrasound, only pathological examination results were used as indicators for LNM, which may weaken the protective effect of ALND when LNM status cannot be clearly demonstrated preoperatively. Although the existing techniques can hardly accurately predict metastatic nodal sites, novel diagnosis methods will enhance the preoperative diagnostic accuracy in the future. Additionally, more studies are needed to validate the efficacy of this novel ALND.

In conclusion, a novel LND strategy was proposed for the optimization of the survival of patients with ESCC undergoing radical 2- or 3-FLND. The ALND proposed in the present study was a metastatic status-dependent LND, which considered the tumor location and metastatic nodal zones. With the exception of patients with high pN stages, patients receiving ALND exhibited improved OS compared with those who did not receive ALND. The competitive advantage of ALND is that when compared with the traditional 2- or 3-FLND, this LND strategy can achieve optimal overall survival without harvesting much more LNs or extending the LND range. Therefore, the present study suggested that the proposed ALND may complement the existing surgical guidelines to improve individualized therapeutic efficacy.

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#### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

#### Authors' contributions

ZH, ZL and XP conceived and designed the study. WC, YC and SY participated in the acquisition of clinical data, were involved in manuscript writing regarding surgical methods and CT scanning, and interpreted the results from a clinical

perspective. ZL, FH, RF and YJ performed the data analysis and interpretation. ZL wrote the manuscript. ZH reviewed and edited the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved.

#### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Fujian Medical University. All patients enrolled in this study provided written informed consent.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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