



# Predicting the Value of Adjuvant Therapy in Esophageal Squamous Cell Carcinoma by Combining the Total Number of Examined Lymph Nodes with the Positive Lymph Node Ratio

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## ABSTRACT

**Background.** The value of adjuvant therapy for esophageal squamous cell carcinoma (ESCC) has been controversial, at least partially due to the lack of efficient criteria for selecting suitable patients. This study aimed to explore the existence of parameters related to lymph node (LN) status that can predict the value of adjuvant therapy in ESCC.

**Methods.** The study included 298 patients with ESCC who had undergone radical esophagectomy with lymphadenectomy. Adjuvant therapy was defined as reception of adjuvant chemotherapy, radiotherapy, or chemoradiotherapy. For the study, LN ratio (LNR), total number of resected LNs (TLNs), and pN stage were selected for Cox regression analyses, including their correlations and prognostic values for survival. Log-rank tests were used to compare the survival rates of the patients with and without adjuvant therapy stratified by pN stage, TLNs, LNR, or their combinations.

**Results.** The independent prognostic factors for survival were TLNs, LNR, and pN stage. Whereas pN stage was significantly related to TLNs and LNR, TLNs were not correlated with LNR. The survival rates between the patients with and those without adjuvant therapy stratified by pN stage, TLNs, or LNR did not differ significantly. We used the median values of TLNs and LNR to group the patients into four groups. The patients in the group with fewer TLNs and higher LNR who had undergone adjuvant therapy showed a significantly better survival than those without adjuvant therapy ( $p = 0.030$ ).

**Conclusions.** In contrast to TLNs, LNR, and pN stage as single factors, the combination of TLNs and LNR can predict the value of adjuvant therapy.

Esophageal cancer (EC) ranks seventh among the most common cancers and sixth among the most common causes of cancer death worldwide, with estimated new cases and deaths annually exceeding 570,000 and 500,000 deaths, respectively.<sup>1</sup> Esophageal squamous cell carcinoma (ESCC) is the predominant histologic type globally, accounting for nearly 90% of the EC cases in Central Asia and in Eastern and Southern Africa.<sup>2</sup>

Surgical resection remains an essential cornerstone in the treatment of EC, but surgery alone results in extremely poor outcomes.<sup>3,4</sup> Locoregional recurrence and distant metastasis are common recurrent patterns after surgery in EC, thereby suggesting the importance of postoperative therapy for some patients.<sup>5,6</sup> However, the values of

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**TABLE 1** The clinicopathologic characteristics of the 298 patients included in the current study

Characteristics	Patients <i>n</i> (%)
Gender	
Male	237 (79.5)
Female	61 (20.5)
Age (years)	
Median (range)	58 (36–78)
≤ 60	192 (64.4)
> 60	106 (35.6)
Location of tumor	
Upper	34 (11.4)
Middle	195 (65.4)
Lower	69 (23.2)
Tumor differentiation	
Well-differentiated	32 (10.7)
Moderately differentiated	202 (67.8)
Poorly differentiated	64 (21.5)
pT stage	
T1a	2 (0.7)
T1b	14 (4.7)
T2	102 (34.2)
T3	140 (47.0)
T4	39 (13.1)
Tumor length (cm)	
Median (range)	3.5 (1–10)
≤ 3	125 (41.9)
3<–≤5	118 (39.6)
> 5	55 (18.5)
pN stage	
N0	112 (37.6)
N1	88 (29.5)
N2	67 (22.5)
N3	31 (10.4)
Adjuvant therapy	
Any type of adjuvant therapy	170 (57.0)
Chemotherapy	103 (34.6)
Radiotherapy	11 (3.7)
Chemoradiotherapy	56 (18.8)
None	128 (43.0)
Total no. of lymph nodes examined	
Median (range)	28 (15–74)
≤ 28	142 (47.7)
> 28	156 (52.3)
Ratio of positive nodes to examined nodes (%)	
Median (range)	4.17 (0–83.78)
≤ 4.17	150 (50.3)
> 4.17	148 (49.7)

postoperative therapies, including adjuvant chemotherapy and radiotherapy, have been controversial,<sup>7–11</sup> at least partially due to the lack of efficient criteria for selecting suitable patients.

An important factor for predicting the prognosis of patients with EC is pN stage, which is based on the number of metastatic lymph nodes (LNs). In addition, pN stage has been shown by several studies to be an effective indicator for postoperative therapy.<sup>12,13</sup> However, accurate identification of the number of metastatic LNs depends on whether the number of resected LNs during surgery is sufficient.

The total number of resected LNs (TLNs) can reflect the extent of lymphadenectomy, and several studies have shown that TLNs are associated with treatment outcomes after EC resection.<sup>14</sup> The LN ratio (LNR), defined as the ratio of metastatic nodes to the examined nodes, is a parameter that considers metastatic LN and TLNs simultaneously. Many studies have explored LNR,<sup>15,16</sup> showing it to be reportedly valuable in predicting the prognosis in ESCC.

The current study simultaneously explored the prognostic values of pN stage, LNR, and TLNs for patients with thoracic ESCC who had undergone three-field lymphadenectomy (3FLND). The study also investigated the influences of these factors on the effectiveness of postoperative therapy.

## MATERIALS AND METHODS

### *Study Population*

We performed a series of studies to explore the clinical and biologic prognostic factors for patients underwent radical esophagectomy with 3FLND at Fudan University Shanghai Cancer Centre between 2001 and 2009.<sup>17–20</sup> The primary inclusion criteria specified thoracic ESCC confirmed by histopathology and classified according to the seventh edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) tumor-node-metastasis (TNM) classification system, involvement of only one primary tumor, no reception of preoperative chemotherapy and/or radiotherapy, 3FLND performed with 15 or more LNs removed, and reception of R0 resection.

Initially, 354 patients were identified. Then, 56 patients were excluded from the analysis because of perioperative deaths (2 patients), no follow-up evaluation (20 patients), or unknown postoperative therapy (34 patients). Finally, 298 patients were included in the study.

The preoperative workup, the surgical procedure, and the follow-up evaluation are described elsewhere.<sup>18,19</sup> Concerning adjuvant therapy, no standard guidelines exist

**TABLE 2** Uni- and multivariate analyses for overall survival (OS) according to the COX proportional hazard regression model

Prognostic factors	<i>p</i> value	<i>p</i> value (univariate)	HR (95% CI) (multivariate)
Gender	0.031	0.049	
Male			1.000
Female			0.619 (0.400–0.958)
Age: years ( $\leq 60$ , $> 60$ )	0.437		
Location of tumor (upper, middle, lower)	0.300		
Tumor differentiation (well, moderately, poorly)	0.347		
pT stage (T1, T2, T3, T4)	0.132		
Tumor length: cm ( $\leq 3$ , $3 < \leq 5$ , $> 5$ )	0.262		
pN stage	$< 0.001$	$< 0.001$	
N0			1.000
N1			1.343 (0.857–2.104)
N2			2.308 (1.368–3.891)
N3			1.012 (0.352–2.911)
Adjuvant therapy (any type of adjuvant therapy, none)	0.632		
Total no. of lymph nodes examined (continuous)	0.008	0.042	0.981 (0.963–0.999)
Ratio of positive nodes to examined nodes (continuous)	$< 0.001$	0.002	1.032 (1.011–1.052)

HR hazard ratio, CI confidence interval

for the postoperative treatment of patients with ESCC in China. Therefore, the treatment options were selected according to tumor stage, physician opinion, hospital practice, and patient desire or economic conditions. Generally, the adjuvant chemotherapy regimen is based on four to six cycles of 5-fluorouracil and cisplatin/oxaliplatin, and the treatment dosage for postoperative radiotherapy is physician-dependent.

In the current study, adjuvant therapy was defined as treatment with adjuvant chemotherapy involving more than two cycles of chemotherapy, radiotherapy involving a radiation dose higher than 45 Gy, or chemoradiotherapy involving radiotherapy and chemotherapy. This study was approved by the Institutional Review Board, which waived the requirement for the written informed consent of individual patients given the retrospective nature of the study.

#### Statistical Analysis

Continuous variables were summarized by descriptive statistics such as means, standard deviations (SDs), medians, and ranges. Categorical variables were tabulated by frequency and percentage. We initially treated TLNs and LNR as continuous variables, performing uni- and multivariate Cox regression analyses to adjust for patient characteristics (age and sex), tumor characteristics (anatomic location, tumor size, histologic grade, American Joint Committee on Cancer [8th edition] pathologic pT, and pN stage), and adjuvant therapy.

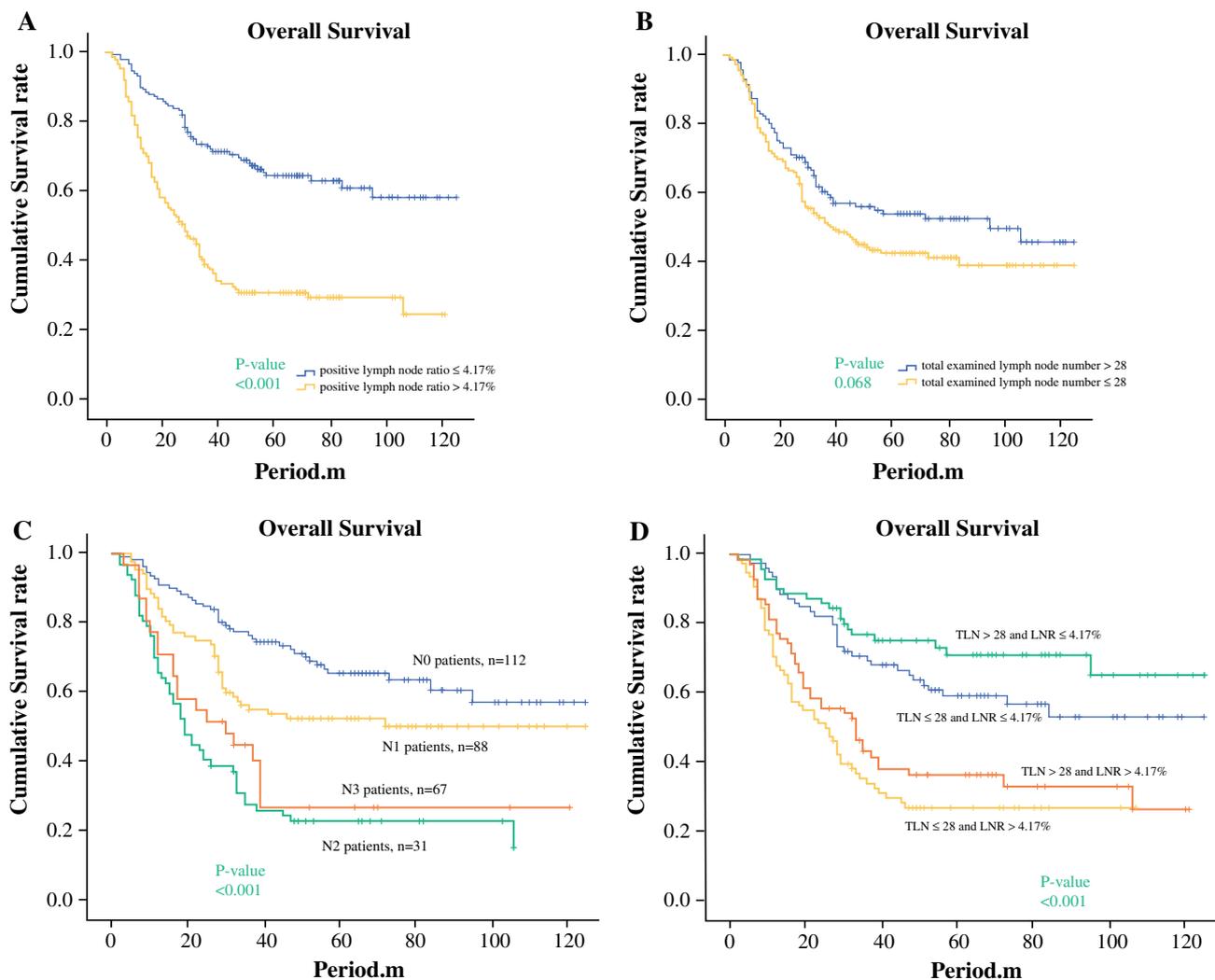
Overall survival (OS) was computed from the date of surgery using Kaplan–Meier estimates, and the log-rank test was used to assess the equality of survival functions. Variables with *p* values lower than 0.10 in the univariate analyses were included in the multivariate Cox proportional hazards model. The cutoff values for TLNs and LNR were defined as medians to stratify the patients.

Correlation analysis was performed on continuous variables using the Pearson correlation test and on the continuous and classified variables using analysis of variance (ANOVA). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (IBM Corp, Armonk, NY, USA), and *p* values of 0.05 or lower were considered statistically significant.

## RESULTS

#### Patient Characteristics

The clinicopathologic characteristics of the study population are summarized in Table 1. Nearly two-thirds of the 298 patients had metastatic LN, accounting for 62.4% of the patients. The TLNs ranged from 15 to 74, with a median of 28. The LNR ranged from 0 to 83.78%, with a median of 4.17%. For 170 (57%) of the patients, adjuvant therapy was performed, including chemotherapy (34.6%), radiotherapy (3.7%), and chemoradiotherapy (18.8%).



**FIG. 1** Log-rank tests of overall survival (OS) for all the patients ( $n = 298$ ). **a** Comparison between the patients with a positive lymph node ratio (LNR) of 4.17% or lower and those with a positive LNR higher than 4.17% ( $p < 0.001$ ). **b** Comparison between the patients

with 28 or fewer lymph nodes (LNs) and those with a total number of lymph nodes (TLNs) exceeding 28 ( $p = 0.068$ ). **c** Classification by pN stage. **d** Classification by a combination of TLNs and positive LNR

#### Prognostic Values of pN Stage, TLNs, and LNR

During a median follow-up period of 36.5 months (range, 2–125 months), the median OS was 51 months (95% confidence interval [CI], 20–81 months), and the 5-year survival rate was 48.1%. The results of the uni- and multivariate analyses are listed in Table 2. On the basis of the univariate analysis, TLNs, LNR, pN stage, and gender were identified as significant prognostic factors.

In the multivariate analysis, TLNs, LNR, pN stage, and gender still were found to be independent prognostic factors for OS. Low TLNs, high LNR, and high pN stage were found to affect survival negatively. Moreover, pN stage was significantly related to TLNs and LNR (Table S1). Therefore, we removed pN stage from the multivariate

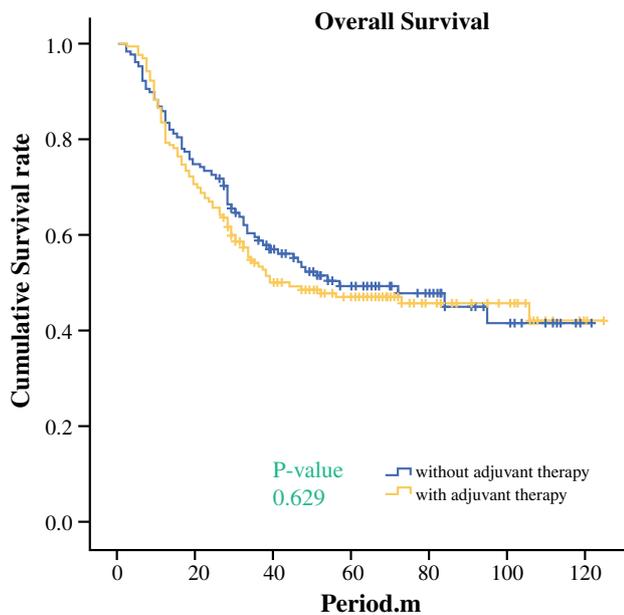
analysis and found that TLNs and LNR remained independent prognostic factors.

Figure 1 shows the survival curves based on the log-rank test according to the LNR stratified by the median ratio (4.17%; Fig. 1a), the TLNs stratified by the median number (28; Fig. 1b), and the N-stage (Fig. 1c).

#### Value of Combining TLNs with LNR

Table 2 shows that adjuvant therapy was not a prognostic factor of OS. The survival difference among the entire population according to adjuvant therapy and use of the log-rank test indicated a  $p$  value of 0.629 (Fig. 2).

On the basis of the possible benefit from adjuvant therapy for some subgroups based on the prognostic factors, we compared the survival rates between patients with



**FIG. 2** Log-rank tests of overall survival (OS) for all the patients comparing those who did and those who did not have postoperative adjuvant therapy ( $n = 298$ ;  $p = 0.629$ )

and without adjuvant therapy stratified by the pN stage, the TLNs, and the LNR and found no significant differences among the groups (Fig. S1). This finding suggested that no single factor could predict the value of adjuvant therapy.

Therefore, we further explored whether the combination of the parameters could present a different result. We initially performed correlation analyses on the three LN-associated factors and found that pN stage was significantly related to TLNs and LNR, whereas TLNs showed no correlation to LNR (Table S1). Therefore, we combined only TLNs and LNR for further analyses. We used the median values of TLNs and LNR to group patients into four groups as follows: (a) LNR higher than 4.17% and TLNs of 28 or fewer ( $n = 78$ ), (b) LNR lower than 4.17% and TLNs fewer than 28 ( $n = 79$ ), (c) LNR lower than 4.17% and TLNs more than 28 ( $n = 71$ ), and (d) LNR higher than 4.17% and TLNs more than 28 ( $n = 70$ ). The survivals of these groups differed significantly ( $p < 0.001$ ; Fig. 1d).

Next, we compared the survival rates of the patients with and without adjuvant therapy in each group and found that the group with an LNR higher than 4.17% and TLNs of 28 or fewer would benefit from adjuvant therapy, whereas the other groups would not (Fig. 3). In this group, the patients who had undergone adjuvant therapy exhibited a significantly higher median survival (28 months; 95% CI, 21–34 months) than those with no adjuvant therapy (median survival, 15 months; 95% CI, 9–20 months;  $p = 0.030$ ; Fig. 3a). This finding indicated that the combination of TLNs and LNR could be a factor in guiding adjuvant therapy.

## DISCUSSION

Lymph node status is important for EC. Our study showed that TLNs, LNR, and pN stage all are prognostic factors for thoracic ESCC treated with radical resection, but that none of these factors can be used alone as indicators for adjuvant therapy. Nevertheless, and more importantly, the subgroup benefiting from adjuvant therapy can be found through combining TLNs and LNR. Therefore, such a combination can guide the selection of suitable patients for adjuvant therapy, but this needs further investigation.

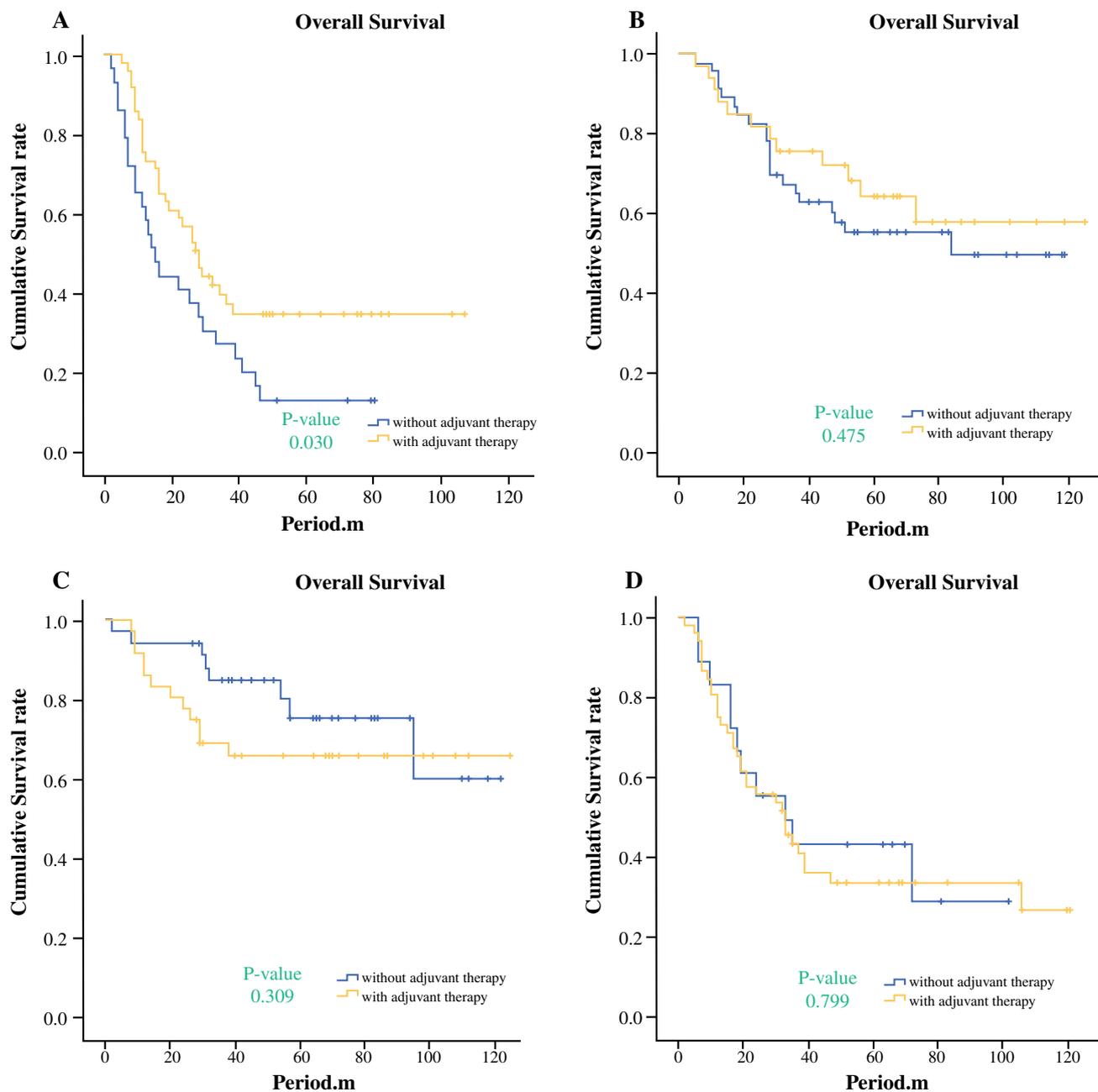
The study showed that pN stage is a parameter that reflects the extent of LN metastases. Since the seventh edition of AJCC, the absolute number of metastatic LNs has been incorporated into the TNM system of ESCC.<sup>21</sup> However, the number of metastatic LNs identified depends on TLNs and thus has some limitations. When the TLNs are insufficient, potentially metastatic LNs may be overlooked, which may lead to “stage migration” and thus to overestimation of patient prognosis.<sup>22</sup> The finding of correlation between pN stage and TLNs in the current study also suggested that TLNs had an influence on pN stage in our cohort.

In addition, LNR is a parameter that reflects the extent of LN metastases, and it simultaneously considers the extent of LN dissection, which differs from pN stage. Therefore, various studies have investigated and demonstrated the advantages of LNR over the metastatic LN number.<sup>15,23</sup> Our finding of no correlation between TLNs and LNR showed that LNR is independent of TLNs. TLNs are also an independent prognostic factor for ESCC, which is consistent with several studies.<sup>14</sup> In addition to correction of “stage migration,” the influence of TLNs on the prognosis of ESCC lies in the potential of TLNs as a marker for the adequacy of surgery, which affects treatment outcomes.

The purpose of adjuvant therapy should be to eliminate subclinical lesions. Theoretically, the existence of subclinical lesions is determined on the basis of tumor behavior and the extent of resection clearance. The extent of LN metastases, as reflected by pN stage and LNR, represents tumor behavior in a way, and TLNs reflect the adequacy of surgery to some extent.

In our study, TLNs, LNR, and pN stage as single factors had no predictive value for adjuvant therapy, whereas the combination of TLNs and LNR did have predictive value. Therefore, the extents of LN metastases and LN dissection are important in predicting the value of adjuvant therapy for patients with ESCC.

This study had several limitations that should be highlighted. Although the operations of all the patients were performed at our institution, many of the adjuvant therapies



**FIG. 3** Log-rank tests of overall survival (OS) comparing the patients who did and those who did not have postoperative adjuvant therapy among those with **a** a lymph node ratio (LNR) higher than 4.17% and total number of resected lymph nodes (TLNs) fewer than

28 ( $n = 78$ ;  $p = 0.030$ ), **b** an LNR lower than 4.17% and TLNs fewer than 28 ( $n = 79$ ;  $p = 0.475$ ), **c** an LNR lower than 4.17% and TLNs more than 28 ( $n = 71$ ;  $p = 0.309$ ), or **d** an LNR higher than 4.17% and TLNs more than 28 ( $n = 70$ ;  $p = 0.799$ )

were administered elsewhere. Thus, the protocols of adjuvant therapies were not uniform, including the chemotherapy regimen, the radiotherapy target volume and dose, and the timing of the adjuvant therapy.

In addition, we put chemotherapy, radiotherapy, and chemoradiotherapy together as adjuvant therapy without separating them for analyses for the following reasons.

First, the number of patients was limited in this study, especially after they were stratified into several groups for analyses, which together with the possible confounding effect between chemotherapy and radiotherapy made the study less powerful. Second, a phase 3 randomized trial showed that adjuvant chemotherapy and radiotherapy had equivalent effects on the survival of patients with ESCC.<sup>24</sup>

Third, adjuvant chemotherapy and radiotherapy have not been approved as a worldwide standard of care for thoracic ESCC, and no solitary evidence shows that a suitable subgroup can benefit from some types of adjuvant therapy.

This study aimed to explore the suitability of some patients for adjuvant therapy through the analysis of clinical factors (i.e., to identify those likely to have subclinical lesions). The reasonable selection of the adjuvant therapeutic approach was beyond our scope.

## CONCLUSIONS

This study corroborated the findings of other studies,<sup>12–15,23</sup> which showed that TLNs, LNR, and pN stage all are prognostic factors for patients with thoracic ESCC who have undergone radical esophagectomy with 3FLND. Moreover, the study showed that the combination of TLNs and LNR can predict the value of adjuvant therapy, whereas TLNs, LNR, and pN stage as single factors cannot. Thus, further investigation is needed.

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**DISCLOSURES** All authors have read and approved the manuscript. We have no financial disclosures. We are not using any copyrighted information, patient photographs, identifiers, or other protected health information in this paper. No text, text boxes, figures, or tables in this article have been previously published or are owned by another party.

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