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RESEARCH

The optimal number of lymph node dissections in three-field lymphadenectomy for esophageal squamous cell carcinoma: a large retrospective study

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Abstract

Background Currently, there is no consensus on the optimal number of lymph node dissections (LNDs) in three-field lymphadenectomy for esophageal squamous cell carcinoma (ESCC). This study aimed to explore the relationship between the LND count and overall survival (OS) in ESCC patients to determine the optimal number of LNDs that confer a survival benefit.

Methods A retrospective analysis was conducted on ESCC patients who underwent three-field lymphadenectomy at Fujian Cancer Hospital from February 2004 to January 2018. The optimal LND number was determined using X-Tile software. Kaplan–Meier survival curves and Cox regression analyses were used to evaluate the relationship between LND count and OS.

Results A total of 1053 ESCC patients who underwent three-field lymphadenectomy were included in this study (median age 58 years [IQR: 52–65], 781 males [74.2%]). Using X-Tile software, 27 was identified as the optimal cutoff value for the number of LNDs. The 5-year OS for the >27 LNDs group was significantly better than that for the ≤27 LNDs group (67.8% vs. 59.8%, $P=0.042$). Multivariate Cox regression analysis confirmed that LND count (≤27 and >27) was an independent protective factor for OS (HR = 0.724; $P=0.004$). Stratified analysis on the basis of TNM stage revealed that in patients with T3-4N0M0 disease (HR = 0.412; $P=0.001$) and T1-2 N + M0 disease (HR = 0.503; $P=0.025$), a greater number of dissected lymph nodes was closely associated with a survival benefit.

Conclusion For ESCC patients undergoing three-field lymphadenectomy, dissecting more than 27 lymph nodes is associated with better prognosis, especially for patients with T3-4N0M0 and T1-2 N + M0 stages.

Keywords Lymph node · Esophageal squamous cell carcinoma · Three-field

Background

Esophageal cancer is the tenth most common cancer worldwide [1]. Although the incidence of esophageal cancer in China has been declining annually, more than 200,000 new cases are still reported each year [2], which poses a significant burden on health in China and globally. The pathological types of esophageal cancer are mainly squamous cell carcinoma (SCC) and adenocarcinoma, with SCC being predominant in Asia [3]. The main treatment approach is comprehensive treatment centered on surgery [4]. Lymph node dissection is generally considered an essential part of surgical treatment and plays a crucial role in identifying lymph node invasion and removing potential lymph node metastases [5]. The impact of the number of lymph nodes dissected on prognosis has been confirmed in studies on

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gastric and colorectal cancers [6–10]. For example, in total gastrectomy, the removal of at least 21 lymph nodes may be associated with a better prognosis [11]. Currently, the NCCN guidelines recommend the dissection of 15 lymph nodes for esophageal cancer [12]. Radical lymph node dissection for esophageal cancer mainly includes two-field and three-field lymphadenectomy [13]. Meta-analyses have shown that three-field lymphadenectomy helps improve long-term survival after surgery in patients with esophageal cancer [14–16]. However, there is no consensus on the optimal number of lymph nodes to be dissected in three-field lymphadenectomy. In this study, we aimed to investigate the relationship between the number of LNDs and OS in ESCC patients. Additionally, we determined the cutoff value to identify the optimal number of LNDs that benefits patient survival.

Patients and methods

We reviewed ESCC patients who underwent three-field lymphadenectomy at Fujian Cancer Hospital from February 2004 to January 2018, with follow-up until March 2023. Due to the retrospective nature of this study, we waived the requirement for individual patient consent. The exclusion criteria were as follows: (a) patients with non-ESCC confirmed by histology; (b) patients with distant metastasis; (c) patients who received neoadjuvant therapy; (d) patients with nonthoracic esophageal cancer; and (e) patients with incomplete resection (R1, R2). Additionally, we excluded patients who died from surgery-related causes (defined as death within one month after surgery). All patients underwent three-field lymphadenectomy via the McKeown approach. Surgical procedures included resection of the primary tumor and lymph node dissection. The anesthetic strategy employed was double-lung ventilation combined with artificial pneumothorax, and the surgical approach was either open surgery or a minimally invasive. The esophagus was mobilized through the right thoracic cavity, followed by mobilization of the stomach through an upper abdominal incision to prepare a tubular stomach. After the cervical esophagus was mobilized through a left cervical incision along the anterior edge of the sternocleidomastoid muscle, the tumor was resected, and the stomach was pulled up to the neck for anastomosis (McKeown). Three-field lymphadenectomy was performed via a cervical–thoracic–abdominal three-incision approach. The two-field lymphadenectomy included mediastinal lymph nodes (mainly including bilateral para-laryngeal nerve lymph nodes, para-tracheal lymph nodes, bilateral para-bronchial lymph nodes, subtracheal lymph nodes, para-esophageal lymph nodes and para-diaphragmatic lymph nodes) and abdominal lymph nodes (mainly including bilateral para-cardia lymph nodes, the lesser curvature of the stomach lymph nodes and left gastric artery lymph nodes). Three-field lymphadenectomy adds cervical dissection to two-field dissection (mainly including bilateral supraclavicular lymph nodes and cervical paratracheoesophageal lymph nodes). A U-shaped incision approximately 14 cm long was made on the neck for three-field lymphadenectomy to dissect the bilateral cervical paratracheoesophageal lymph nodes, mainly the bilateral recurrent laryngeal nerve lymph nodes. The bilateral supraclavicular lymph node dissection ranged from the omohyoid muscle up to the upper edge of the clavicle, internally to the internal jugular vein, and externally to the accessory nerve [17]. Lymph nodes were identified, separated, counted, and submitted for examination intraoperatively by the surgeon. Subsequently, the pathologist re-evaluated and recounted the lymph nodes and provided a pathological report, including the assessment of lymph node metastasis. Postoperatively, patients followed up every 3 months for 2 years and then every 6 months until the last follow-up in March 2023 or death. Follow-up was conducted through outpatient visits or telephone follow-up. OS was defined as the time from surgery to the occurrence of a death event or the last follow-up. Pathological staging was based on the 8th edition of the AJCC/UICC staging system.

Statistical analysis

The Lilliefors test was used to examine the normality of the variable distributions. Continuous variables are described as medians with interquartile ranges (IQRs) and were compared using the student t-test or the Wilcoxon rank-sum test. Categorical variables are described as percentage frequencies (%) and were compared using Pearson's chi-square test or Fisher's exact test. We used X-tile software to determine the optimal cutoff value for LND and applied univariate and multivariate Cox proportional hazards regression models to investigate the correlation between LND count and OS. The hazard ratio (HR) and 95% confidence interval (95% CI) was calculated via univariate and multivariate Cox proportional hazards regression analyses. Univariate analysis was used to evaluate the impact of clinicopathological factors on overall survival. Multivariate analysis was performed after adjusting for other factors to identify the number of LNDs as an independent prognostic indicator. Variables with $P < 0.05$ or those identified as prognostic in the univariate analysis (e.g., sex and age) were included in the multivariate analysis. Kaplan–Meier survival analysis and the log-rank test were used to compare survival curves between different groups. All the statistical tests were two-sided, with $P < 0.05$ considered statistically significant. Statistical analyses were performed via SPSS Statistic 29.0 software (IBM SPSS, Inc., Chicago, IL, USA) and X-tile version 3.6.1 (http://www.tissuearray.org/rimmlab).

Results

Patient characteristics

A total of 1,053 patients with ESCC underwent esophagectomy and three-field lymphadenectomy. The median age of the patients was 58 years (IQR: 52–65 years). Most patients were male (74.2%), with tumors located primarily in the middle thoracic segment (67.8%). The pathological stage was predominantly T3 (59.1%), and nearly half of the patients had no lymph node metastasis (42.6%). According to pathological TNM staging, the number of patients with stages I, II, III, and IVa disease were 150 (14.2%), 360 (34.2%), 430 (40.8%), and 113 (10.7%), respectively. The degree of tumor differentiation was mainly moderate (75.0%), with approximately 20% of patients exhibiting lymphovascular invasion. The median number of LNDs was 29, and approximately half of the patients received postoperative adjuvant chemotherapy (53.6%). In this study, the overall 1-year, 3-year, and 5-year survival rates for the patients were 91.3%, 70.2%, and 63.9%, respectively. (Table 1)

Table 1 Clinicopathologic characteristics of patients

Parameter	Study cohort
Age (IQR, y)	58 (52–65)
Sex (n, %)	
Male	781 (74.2%)
Female	272 (25.8%)
T stage (n, %)	
T1	174 (16.5%)
T2	185 (17.6%)
T3	622 (59.1%)
T4	72 (6.8%)
N stage (n, %)	
N0	486 (46.2%)
N1	351 (33.3%)
N2	145 (13.8%)
N3	71 (6.7%)
pTNM stage (n, %)	
I stage	150 (14.2%)
II stage	360 (34.2%)
III stage	430 (40.8%)
IVa stage	113 (10.7%)
Tumor location (n, %)	
Upper thoracic	174 (16.5%)
Middle thoracic	714 (67.8%)
Lower thoracic	165 (15.7%)
Differentiation (n, %)	
Well	123 (11.7%)
Moderate	794 (75.4%)
Poor	136 (12.9%)
LND count (IQR)	29 (22–39)
Postoperative adjuvant therapy (n, %)	
No	564 (53.6%)
Yes	489 (46.4%)
Lymphovascular invasion (n, %)	
No	831 (78.9%)
Yes	222 (21.1%)
Overall survival rate (%)	
1-year	91.3%
3-year	70.2%
5-year	60.9%

Optimal cutoff value for lymph node dissection

Using X-tile software, we determined the optimal cutoff value for the number of LNDs to be 27 (≤27 LNDs, > 27 LNDs) (χ^2 = 4.1489, P=0.04288) (Supplemental Figure). Furthermore, to validate this optimal cutoff value, we divided the patients into two groups based on the number of LNDs ranging from 11 to 50 and performed a log-rank test, resulting in 40 chi-square values. Among these, > 27 LNDs was consistently identified as the optimal cutoff, with the highest chi-square value of 4.160 and P=0.041 (Supplemental Table). Thus, all patients were categorized into two groups (≤27 LNDs, n=470; > 27 LNDs, n=583). Our results revealed that within this study cohort, the 3-year survival rates for the >27 LNDs subgroup and the ≤27 LNDs subgroup were 72.5% and 67.6%, respectively; the 5-year survival rates were 67.8% and 59.8%, respectively. We found a significant difference between the >27 LNDs group and the ≤27 LNDs group, with an unadjusted HR of 0.803 and 95% CI of 0.650–0.992; P=0.042 (Fig. 1). The NCCN guidelines recommend dissecting at least 15 lymph nodes. We grouped the patients based on having≥15 LNDs and <15 LNDs, resulting in a chi-square value of 3.9216 and P=0.048, with a chi-square value lower than the optimal cutoff of 27 nodes (Fig. 2).

Univariate and multivariate analyses

As shown in Table 2, univariate analysis revealed that sex (P=0.005), age (P=0.039), T stage (P<0.001), N stage (P<0.001), adjuvant therapy (P<0.001), lymphovascular invasion (P<0.001), and the number of LNDs (P=0.042) were significantly associated with survival in patients with ESCC. Further multivariate analysis demonstrated that having>27 LNDs was an independent protective factor for the prognosis of ESCC patients who underwent three-field lymphadenectomy (HR=0.724, 95% CI 0.582–0.900; P=0.004). Other independent prognostic factors identified

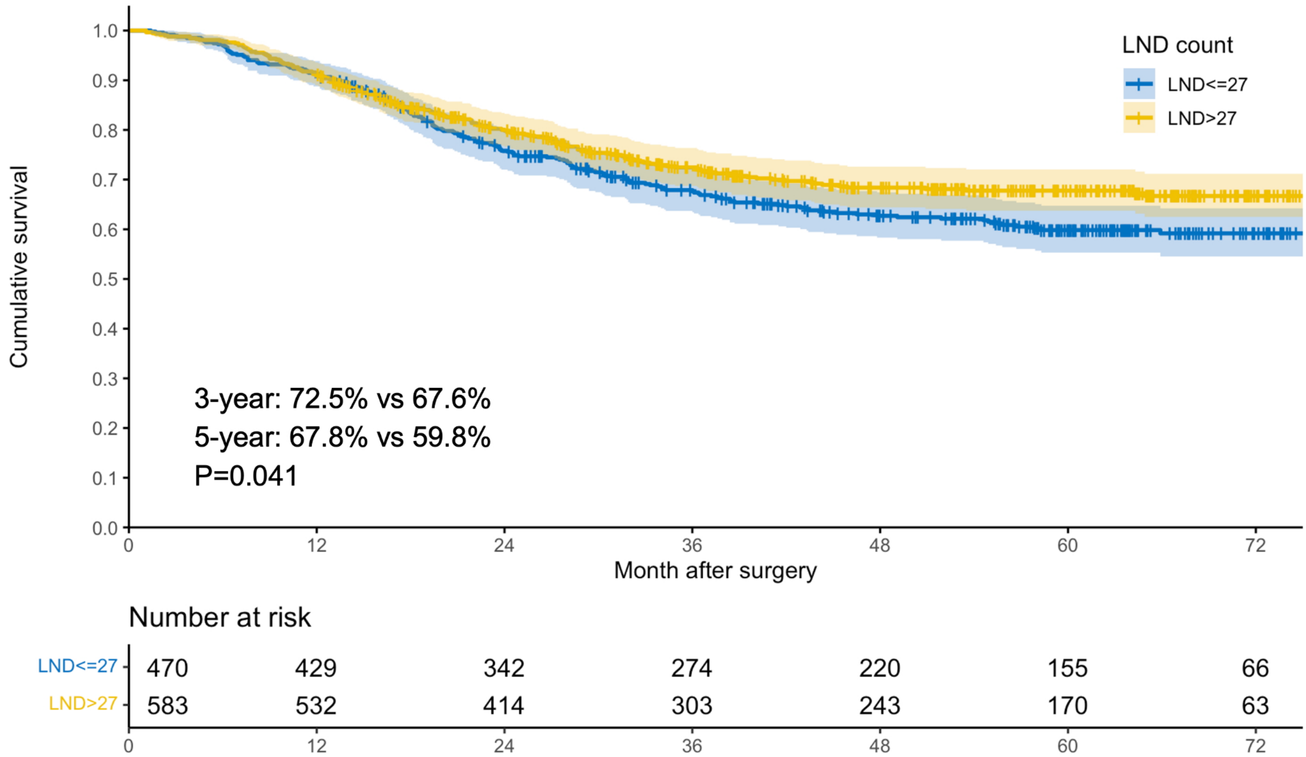

Fig. 1 Overall survival curves stratified by the optimal LND count (<=27 vesus>27) for esophageal squamous cell carcinoma patients

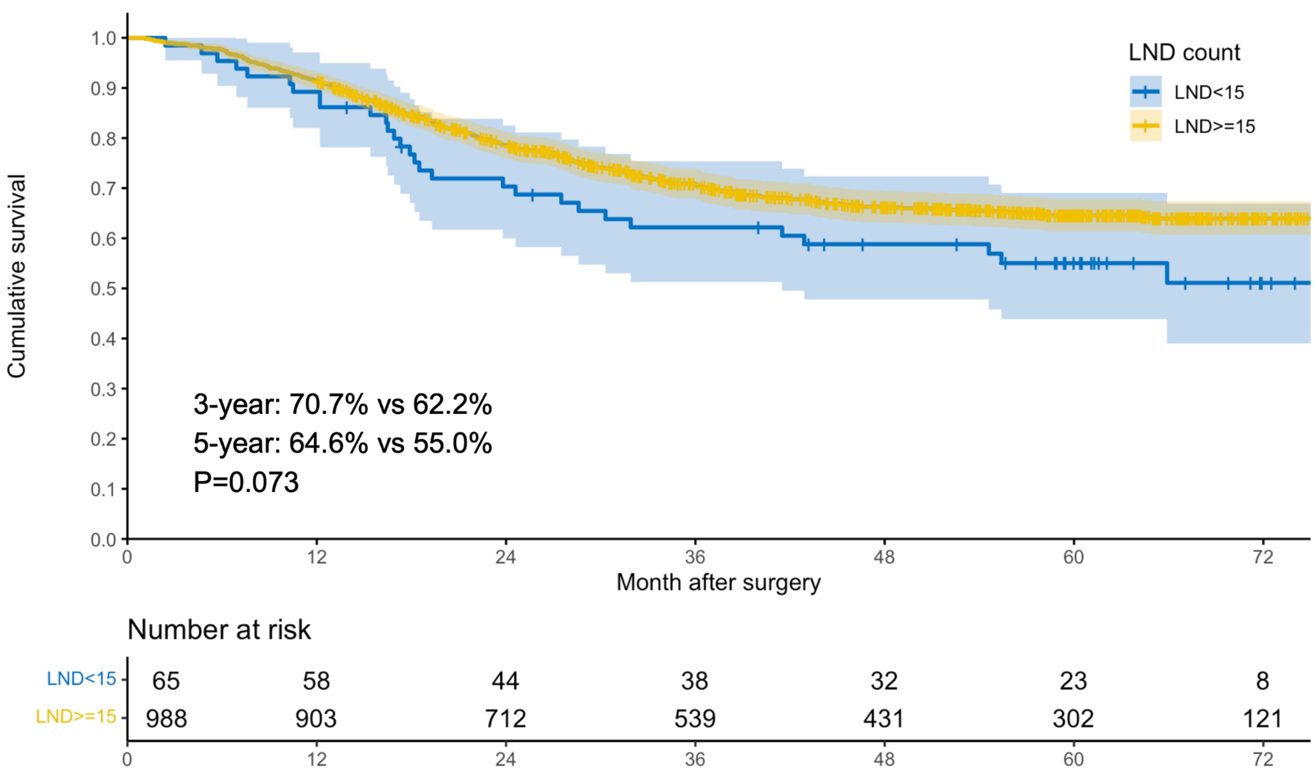

Fig. 2 Overall survival curves stratified by LND count (<15 vesus>=15) for esophageal squamous cell carcinoma patients

Table 2 Univariable and multivariable Cox regression analyses for prognostic factors in ESCC patients who underwent three-field lymphadenectomy

	Univariable analyses			Multivariable analyses		
	HR	95%CI	*P*-Value	HR	95%CI	*P*-Value
Sex						
male	1	reference		1	reference	
female	0.686	0.528–0.892	0.005	0.771	0.590–1.009	0.059
Age						
≤60	1	reference		1	reference	
>60	1.251	1.011–1.548	0.039	1.477	1.189–1.835	<0.001
Tumor location						
Upper	1	reference		1	reference	
Middle	1.074	0.807–1.429	0.624	1.031	0.771–1.380	0.836
Lower	0.641	0.424–0.968	0.035	0.649	0.427–0.987	0.043
pT stage						
T1	1	reference		1	reference	
T2	2.774	1.595–4.823	<0.001	1.955	1.113–3.434	0.020
T3	4.472	2.733–7.316	<0.001	2.944	1.778–4.875	<0.001
T4	8.734	4.998–15.263	<0.001	4.565	2.555–8.157	<0.001
pN stage						
N0	1	reference		1	reference	
N1	2.765	2.102–3.637	<0.001	2.577	1.920–3.460	<0.001
N2	3.896	2.840–5.345	<0.001	3.768	2.509–5.659	<0.001
N3	8.726	6.147–12.387	<0.001	8.252	5.292–12.869	<0.001
Tumor differentiation						
Well	1	reference		1	reference	
Moderate	1.298	0.903–1.865	0.159	1.076	0.743–1.559	0.699
Poor	1.687	1.097–2.594	0.017	1.091	0.699–1.703	0.701
Postoperative adjuvant therapy						
No	1	reference		1	reference	
Yes	1.991	1.605–2.470	<0.001	1.278	0.950–1.718	0.105
Lymphovascular invasion						
No	1	reference		1	reference	
Yes	1.814	1.435–2.294	<0.001	1.287	1.006–1.648	0.045
LND count						
≤27	1	reference		1	reference	
>27	0.803	0.650–0.992	0.042	0.724	0.582-0.900	0.004

ESCC esophageal squamous cell carcinoma, HR hazard ratio, CI confidence interval, LND lymph node dissection

in the multivariate analysis included age, T stage, N stage, and lymphovascular invasion (all $P<0.05$).

Prognostic value of the optimal number of LNDs in different stages

To evaluate the impact of LNDs count on different TNM stages, we used Kaplan–Meier analysis to plot survival curves. The results indicated that the number of LNDs could identify subgroups of ESCC patients with poorer prognosis across different TNM stages. In both stage I and stage IV patients, the prognoses were similar between the ≤27 LNDs group and the >27 LNDs group ($n=150$, $P=0.855$; $n=113$, $P=0.275$). However, in stage II and stage III patients, the >27 LNDs group had a better prognosis than the ≤27 LNDs group did ($n=360$, $P<0.001$; $n=430$, $P=0.038$) (Fig. 3). Stratified analysis based on N stage revealed that in the N0 stage, patients with >27 LNDs had a significant survival benefit compared with those with ≤27 LNDs ($P=0.001$). In contrast, in the N+stage, survival was comparable between patients with >27 LNDs and those with ≤27 LNDs ($P=0.293$) (Fig. 4). We further divided N0 stage patients into T1-2N0M0 and T3-4N0M0 and N+stage patients into T1-2 N+M0 and T3-4 N+M0. The analysis revealed that in the T3-4N0M0 group (HR=0.412, 95% CI: 0.241–0.705; $P=0.001$) and the T1-2 N+M0 group (HR=0.503, 95% CI: 0.276–0.919; $P=0.025$), patients with >27 LNDs had significantly better overall survival than those with ≤27 LNDs. However, in the T1-2N0M0 and T3-4 N+M0 groups, the prognosis was comparable between the two LND groups (both $P>0.05$, Fig. 5).

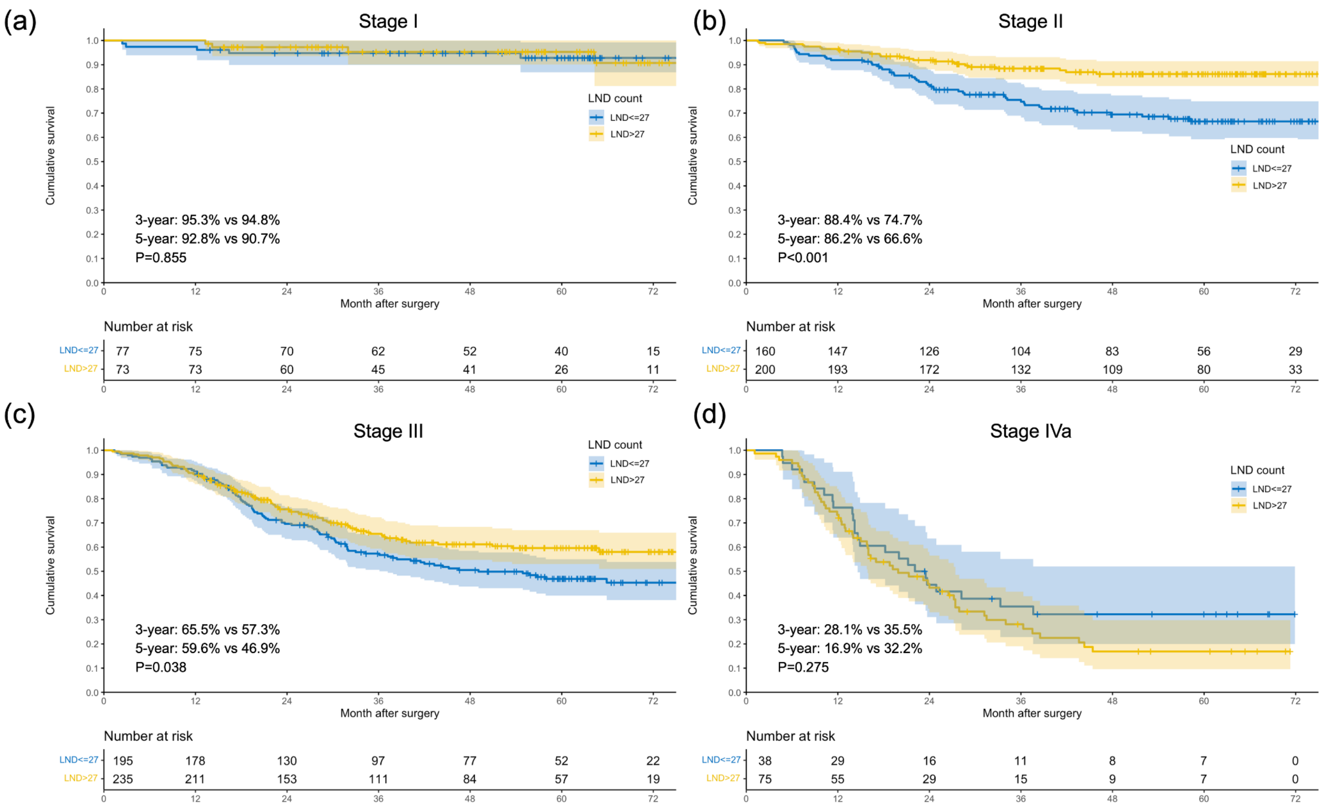

Fig. 3 Overall survival curves for esophageal squamous cell carcinoma patients according to the optimal number of lymph node dissection in the cohort of pathological Stage I (**a**), $n = 150$; Stage II (**b**), $n = 360$; Stage III (**c**), $n = 430$; Stage IVa (**d**), $n = 113$

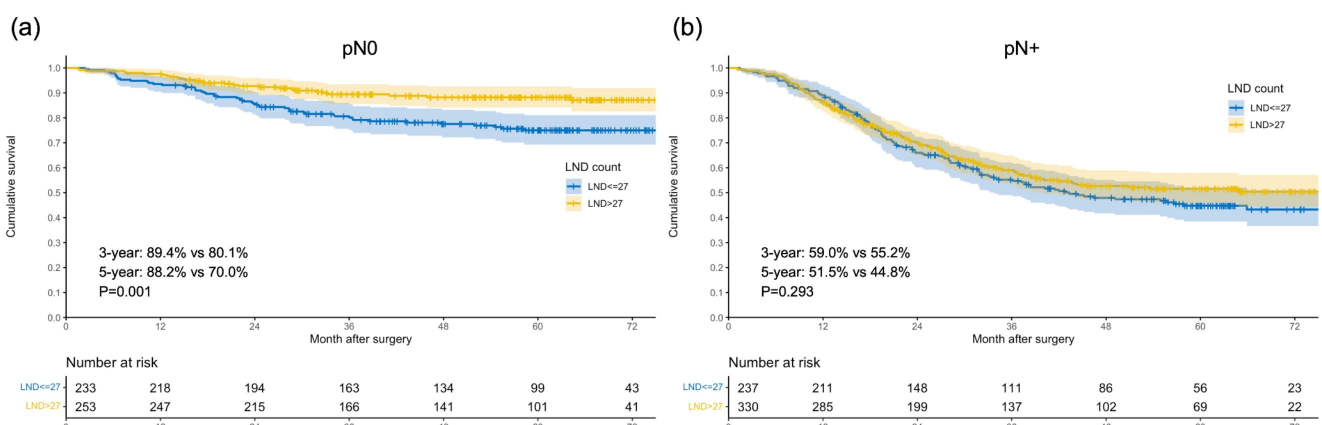

Fig. 4 Overall survival curves for esophageal squamous cell carcinoma patients according to the optimal number of lymph node dissection in the cohort of pathological N0 (**a**), $n = 486$; N+ (**b**), $n = 567$

Discussion

Previous studies have demonstrated a close correlation between the number of LNDs and the prognosis of patients with esophageal cancer [18–22]. However, there are currently no studies specifically addressing the optimal number of lymph nodes to be dissected in three-field lymphadenectomy for ESCC. In this study, we identified 27 as the optimal number of LNDs. Patients with more than 27 lymph nodes dissected exhibited significantly better long-term survival, particularly those with T3-4N0M0 and T1-2 N+M0 stages.

Previous studies have shown a close relationship between the number of LNDs and the prognosis of patients with esophageal cancer. Hai-Quan Chen et al. suggested that an insufficient number of LNDs might lead to residual occult lesions, which are associated with early recurrence of the disease [23, 24]. However, an excessive number of LNDs could result in prolonged surgery time, increased

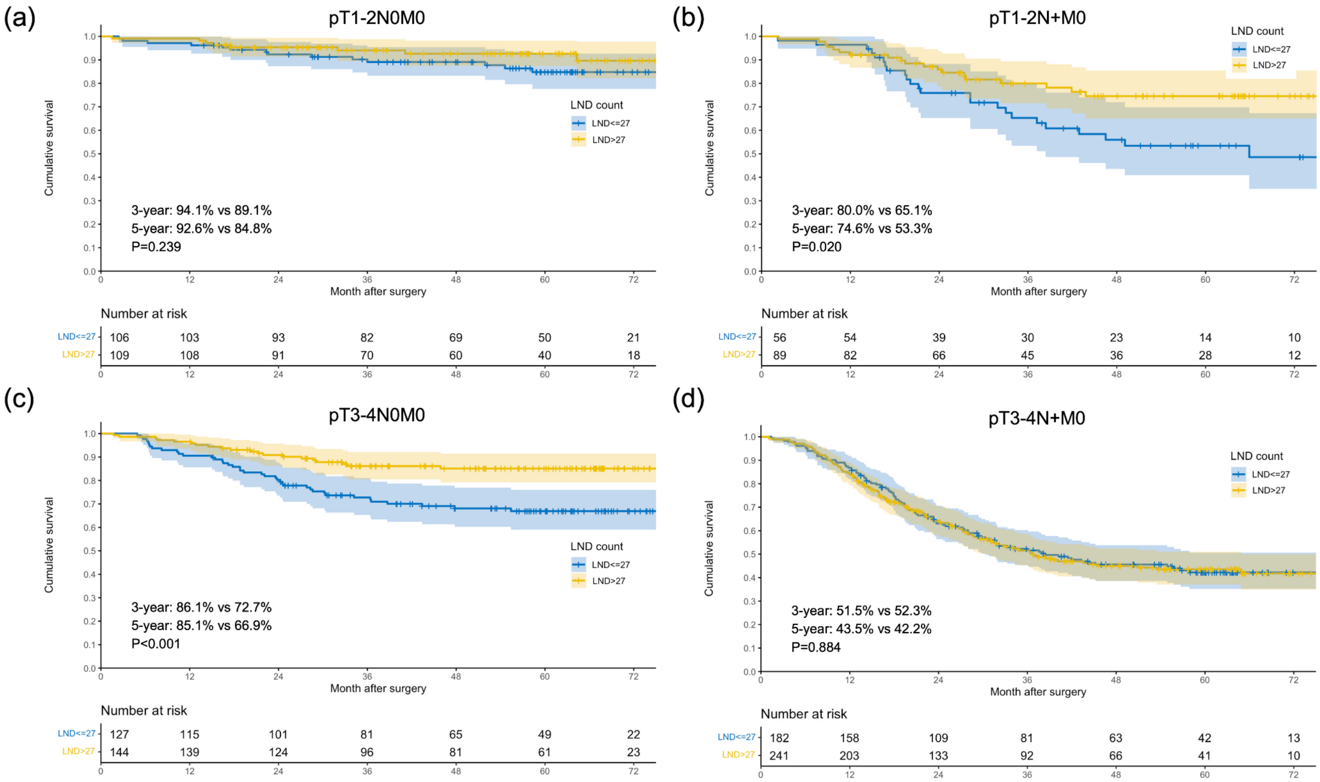

Fig. 5 Overall survival curves for esophageal squamous cell carcinoma patients according to the optimal number of lymph node dissection in the cohort of pathological T1-2N0M0 (**a**), $n=215$; T1-2 N+M0 (**b**), $n=144$; T3-4N0M0 (**c**), $n=271$; T3-4 N+M0 (**d**), $n=423$

postoperative complications, and reduced quality of life [10, 11]. The optimal number of LNDs for esophageal cancer remains controversial. A retrospective study of the SEER database indicated that patients who had more than 12 lymph nodes examined had significantly lower mortality rates than those with 0 to 11 nodes examined. The lowest mortality was observed in patients with more than 30 lymph nodes examined ($n=4882$) [25]. Another report from the WECC database revealed that more extensive lymph node dissection was associated with improved survival in all patients with node-positive cancer ($n=4627$) [26]. Most studies on the optimal number of LNDs in ESCC patients have focused on two-field lymphadenectomy, with surgical approaches including the Sweet, Ivor–Lewis, and McKeown procedures [5, 27, 28]. However, there is currently no research specifically investigating the optimal number of LNDs for three-field lymphadenectomy. The current guidelines recommend that esophageal cancer patients should not have less than 15 lymph nodes dissected in, but this conclusion is not based on the pathological characteristics of Asian patients, where SCC predominates.

In this study, all included patients had SCC, and three-field lymphadenectomy via the McKeown approach (cervical-thoracic-abdominal) was performed. Multivariate Cox analysis confirmed that the number of LNDs was an independent factor influencing long-term survival after adjusting for other confounding factors, such as sex, age, tumor location, pT stage, pN stage, and differentiation grade. This finding aligns with those of previous studies. San-Gang Wu et al. demonstrated that lymph node dissection could improve survival rates in patients undergoing esophagectomy [29]. Similarly, Roderich E et al. reported that a higher total lymph node dissection count and a higher negative lymph node dissection count were associated with better OS and the lowest 90-day mortality rate [30]. Similarly, a study by Qi-Xin Shang et al. concluded that three-field lymphadenectomy results in better OS for esophageal cancer patients. Moreover, three-field lymphadenectomy is considered more suitable for treating esophageal cancer with cervical and/or upper mediastinal lymph node metastasis, regardless of tumor histology and location [31].

A highlight of this study is the detailed stratified analysis we conducted. According to the TNM staging, patients in stages II and III might benefit from an increased number of LNDs, whereas N0 patients, as opposed to N+patients, could be the population that benefits. Further subgroup analysis revealed that for patients with T1-2N0M0 and T3-4 N+M0 disease, an increase in the number of LNDs did not improve survival. These findings suggest that for patients in the early stages without lymph node metastasis and those in the advanced stages with lymph node metastasis, enhancing lymph node dissection might not prolong OS. However, for patients with T1-2 N+M0 and T3-4N0M0 disease, an increase in the number of lymph nodes dissected was closely associated with survival benefits. Previous studies have reported similar findings. For example, Yu-Zhen Zheng et al. reported that aggressive surgery for patients in stages N2-3 did not improve survival rates [32]. In contrast, Chang Hyun Kang's study demonstrated that a broader range of lymph node dissection was associated with higher long-term survival rates than limited lymph node dissection was, especially in N0 patients [33]. Therefore, for patients undergoing three-field lymphadenectomy with T1-2 N+M0 and T3-4N0M0 staging, thorough and standardized lymph node dissection contributes significantly to survival benefits.

Limitations

However, this study also has several limitations. First, as a retrospective study, there is potential for selection bias, particularly since only patients with squamous cell carcinoma were included, which may limit the generalizability of the findings. Second, due to the broad study timeframe, neoadjuvant therapy for advanced esophageal cancer was not incorporated into clinical guidelines during the earlier years, resulting in a lack of relevant cases and the exclusion of patients who received such therapy. Furthermore, the absence of sufficient data to evaluate cancer-specific survival (CSS) means that OS may have been influenced by non-cancer-related factors. Third, studies suggest that surgeons who perform lymph node dissection at the back table or submit lymph nodes individually packaged by nodal station tend to achieve higher retrieval counts [34], which may partly account for the relatively high median lymph node count observed in this study.

To address these limitations, Future studies should include more diverse cohorts, including patients with different histological subtypes, to enhance the generalizability of the findings. Additionally, it is crucial to include patients receiving neoadjuvant therapy in order to further investigate the optimal number of lymph nodes to be removed after such treatment and to identify potential populations that might benefit. Furthermore, standardized protocols for lymph node dissection and counting should be established to ensure consistency in reporting and minimize variations related to surgical techniques and pathological processing.

Conclusion

In conclusion, our study indicates that the number of LNDs is an important independent factor influencing the prognosis of thoracic ESCC patients undergoing three-field lymphadenectomy. Dissecting more than 27 lymph nodes is associated with better overall survival, particularly for patients with T3-4N0M0 and T1-2 N+M0 ESCC. However, in the current era where neoadjuvant and adjuvant therapies play a significant role, further research is needed to validate the universal applicability of the optimal number of lymph node dissections.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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