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ORIGINAL RESEARCH

# Number of Resected Lymph Nodes and Survival Status in Node-Negative Esophageal Squamous Cell Carcinoma: A Cohort Study

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**Objective:** To explore the association between survival status and the number of resected lymph nodes in node-negative esophageal squamous cell carcinoma(ESCC) after surgical treatment.

**Methods:** This was a retrospective observational cohort study and data were obtained from the Surveillance, Epidemiology, and End Results program (SEER) and TaiZhou hospital in China. The data for subjects with negative lymph nodes and no distant metastasis (pN0M0) after post-operative pathology were screened. The nonlinear relationship between resected lymph node number and survival status in node-negative ESCC was conducted using restricted cubic spline regression analysis. The association between the number of resected lymph nodes and survival status in node-negative ESCC was evaluated by Cox proportional hazards regression models. Subgroup analysis based on different subgroups was also performed.

**Results:** A total of 999 subjects were included in the study. Restricted cubic spline regression was used to show a U shaped association between the number of resected lymph nodes and survival status in node-negative ESCC, with low count associated with a decreased survival. To elucidate the association, we adjusted for age, sex, race, T stage, TNM (tumor node metastasis classification), location, grade, chemotherapy, and radiotherapy. As the resected lymph node number increased by one node, the survival status was improved by 2% (Hazard ratio(HR) = 0.98, 95% confidence interval (CI) 0.98–0.99). Sensitivity analysis indicate that the effect size and direction in different subgroups are consistent, the results is stability in SEER.

**Conclusion:** A low count of resected lymph nodes correlated with reduced survival in patients with ESCC, where resecting 25 to 28 or more nodes is considered optimal. Larger prospective studies are warranted to confirm these findings.

**Keywords:** number of lymph node resection, survival status, cohort study, nonlinear relationship, node-negative esophageal squamous cell carcinoma

## Introduction

Esophageal cancer (EC) ranks as the sixth most prevalent cancer globally, with approximately 604,000 new cases and 544,000 deaths annually.[1] Despite significant advancements in treatment modalities such as surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy, the prognosis for EC remains poor. The primary curative treatment for resectable esophageal squamous cell carcinoma (ESCC) is esophagectomy, which ideally includes a thorough lymph node resection (LNR) to achieve an R0 resection.[2,3]

The status of lymph nodes is a critical determinant of prognosis and survival in EC patients. Effective LNR allows for the identification of metastatic lymph nodes, guiding adjuvant therapy decisions. However, there is no consensus on the standardized protocol for LNR, particularly regarding the optimal number of lymph nodes that should be excised to ensure an R0 resection in ESCC.[4–6] Current guidelines vary, leaving a gap in the standardization of surgical practices.



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Given the heterogeneity in lymph node dissection practices and the lack of a clear standard, this study aims to explore the relationship between the number of lymph nodes resected and survival outcomes in node-negative ESCC following esophagectomy. Establishing a minimum number of lymph nodes required for an effective LNR could standardize surgical procedures and potentially improve patient outcomes.

# Methods and Materials

## Patient Enrolment

Data were obtained from the SEER and TaiZhou hospital database. The SEER 18 registries cover approximately 30% of the US population.(https://seer.cancer.gov). Data were extracted from the SEER database for 932 ESCC patients who underwent surgical resection between 2004 and 2020 and whose post-operative pathology suggested no lymphatic metastases. Then, data of 67 ESCC patients with lymph node-negative postoperative pathology were extracted from TaiZhou hospital in China from 2014 to 2020 to further analyze the minimum number of lymph nodes that should be removed during surgery for patients with lymph node-negative ESCC. For Dataset TaiZhou hospital, the last follow-up date was may 6, 2022.

The inclusion criteria were as follows: 1. Underwent an esophagectomy; 2. ESCC confirmed by postoperative pathological examination; 3. Dissection of at least one lymph node; 4. All lymph nodes revealed negative and no metastasis; The exclusion criteria were as follows: 1. Presence of distant metastases; 2. History of the tumor. The study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province, which is affiliated with Wenzhou Medical University. The approval number for this study is L2024-01-63-01. All procedures were performed in accordance with the guidelines set by the committee. The Ethics Committee of Taizhou Hospital waived the requirement for patient consent to review their medical records due to the retrospective nature of the study. Patient data confidentiality was strictly maintained, and all data were anonymized and handled in compliance with the Declaration of Helsinki.

# Measurement

The covariates were selected based on investigations and previous clinical experience. The following variables were included: age, gender (male and female), race (white, black, others), pathological characteristics (total number of removed LNs, T stage, andTNM), location (lower third, middle third, upper third, overlapping), grade (I: well differentiated, II: moderately differentiated, III/IV: poorly differentiated and undifferentiated), chemotherapy (chemotherapy and no chemotherapy), and radiotherapy (radiotherapy and no radiotherapy), Survival time. Each patient's survival or death was recorded in the database. At the end of the follow-up, survival status can be determined by death or not.

# Statistical Analysis

Data are presented as mean plus or minus SD, median (interquartile range), or mean (interquartile range). Student's t-tests or Mann–Whitney *U*-tests were used to compare variables between groups based on their normality, while Fisher's Exact tests were used to compare categorical variables.

An analysis of categorical variables depicts the percentage or frequency value. To find the nonlinear relationship between survival status and the number of resected lymph nodes, restricted cubic spline regression was used. A two-piecewise linear regression approach was adopted to explore the threshold effect of the number of resected lymph nodes on survival status. A smoothed curve was used to calculate the inflection point if the effect of the number of resected lymph nodes on survival status was obvious. Next, we performed subgroup analyses to validate the robustness of the results, then subjected the resulting subgroup modifications and interactions to likelihood ratio tests. Cox proportional hazard regression models were adopted to explore the associations between survival status and the number of resected lymph nodes in node-negative esophageal squamous cell carcinoma after surgical treatment. According to the recommendations of the STROBE statement,[7] we reported the results in non-adjusted, minimally adjusted, and fully adjusted analyses. The subjects were divided into three groups based on the number of resected lymph nodes, and trend tests were conducted using linear regression. Furthermore, a subgroup analysis was conducted to find the association between Number of Resected Lymph Nodes and Survival Status in Node-negative ESCC within each subgroup. Analyses of interactions within the data were carried out sequentially, focusing on one interaction at a time. In instances where the comparator group reported zero events and the partial likelihood achieved convergence at a finite value, we employed Firth's penalization to correct the partial likelihood within the analysis of the TaiZhou hospital cohort.

All analyses were carried out using statistical packages developed in R software version 4.2.2 (http://www.r-project.org, The R Foundation) and Free Statistics software version 1.9. To illustrate statistical significance, a two-sided $p < 0.05$ was used.

## Results

A total of 932 subjects in SEER database and 67 subjects in TaiZhou hospital database were enrolled in this study (Figure 1). For the entire population in SEER database, the average age was 63.5 years, and the median follow-up duration was 29 months. A summary of the participants' baseline parameters, divided into tertiles based on the number of lymph node resections (≤8, 8–17, ≥17), is outlined in Table 1. A total of 509 patients had died at the last follow-up. Compared to the other two groups (T1 and T2), participants in the T3 group (T3 ≥17) had a significantly better survival status, and we discovered no statistically significant differences between the groups in terms of location, grade, T stage, TNM, chemotherapy, or radiotherapy.

The median follow-up duration was 13.8 months in TaiZhou hospital database. Patients in the resected LNs Q1 group were compared to those in the other groups, found that the latter were more likely to be younger and no statistically significant differences between the groups in terms of location, grade, T stage, TNM, chemoradiotherapy (Table 2).

Restricted cubic spline smoothing curve fitting was adopted to explore the relationship between the number of resected lymph nodes and survival status, and the results demonstrated that there is a U-shape association between the number of resected LNs and survival status. A low count of resected lymph nodes was associated with a decreased survival for patients with ESCC. In the SEER database, the optimal number of lymph nodes resected for esophageal cancer patients is greater than 25, whereas in the Taizhou Hospital database, the optimal number is more than 28. (Figure 2).

Table 3 displays the relationship between survival status and the number of resected lymph nodes. In the crude model, the HR (95% CI) for the number of resected lymph nodes with survival status was 0.98 (0.97, 0.99), while the HR (95% CI) following age and sex adjustments was 0.98 (0.97, 0.99), and the HR (95% CI) following adjustment for age, sex,

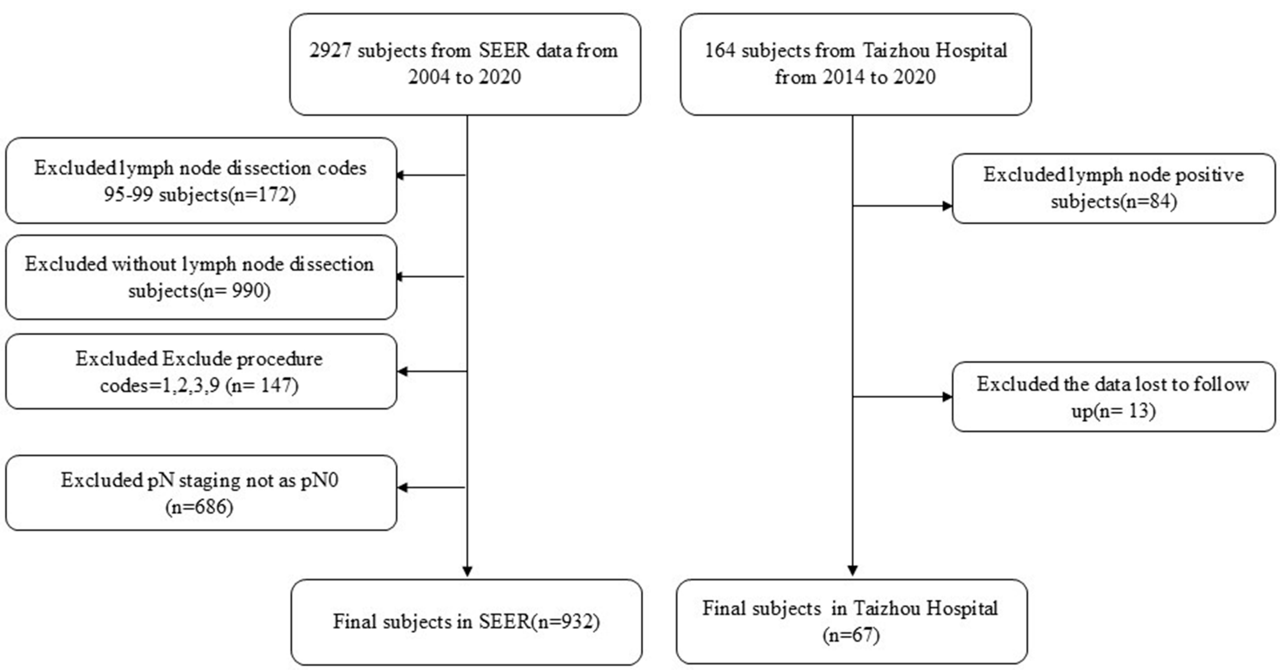


**Figure 1** Flow chart of patients disposition.

**Table 1** Baseline Characteristics of Patients in SEER

| Variables | Overall | T1 (≤8) | T2 (8–17) | T3 (≥17) | p |
|---|---|---|---|---|---|
| | n = 932 | n = 284 | n = 320 | n = 328 | |
| Age (Mean ± SD) | 63.5 ± 9.3 | 63.4 ± 9.2 | 62.7 ± 9.1 | 64.5 ± 9.6 | 0.058 |
| Gender, n (%) | | | | | 0.178 |
| Male | 553 (59.3) | 179 (63) | 178 (55.6) | 196 (59.8) | |
| Female | 379 (40.7) | 105 (37) | 142 (44.4) | 132 (40.2) | |
| Race, n (%) | | | | | < 0.001 |
| Black | 151 (16.2) | 64 (22.5) | 61 (19.1) | 26 (7.9) | |
| White | 679 (72.9) | 200 (70.4) | 234 (73.1) | 245 (74.7) | |
| Others | 102 (10.9) | 20 (7) | 25 (7.8) | 57 (17.4) | |
| Location, n (%) | | | | | 0.718 |
| Up | 67 (7.2) | 24 (8.5) | 25 (7.8) | 18 (5.5) | |
| Middle | 415 (44.5) | 121 (42.6) | 148 (46.2) | 146 (44.5) | |
| Low | 362 (38.8) | 113 (39.8) | 120 (37.5) | 129 (39.3) | |
| Mixed | 88 (9.4) | 26 (9.2) | 27 (8.4) | 35 (10.7) | |
| Grade n (%) | | | | | 0.738 |
| High | 82 (8.8) | 26 (9.2) | 23 (7.2) | 33 (10.1) | |
| Middle | 443 (47.5) | 132 (46.5) | 155 (48.4) | 156 (47.6) | |
| Low | 304 (32.6) | 99 (34.9) | 104 (32.5) | 101 (30.8) | |
| Stage T n (%) | | | | | 0.876 |
| T1 | 280 (30.0) | 88 (31) | 94 (29.4) | 98 (29.9) | |
| T2 | 179 (19.2) | 52 (18.3) | 59 (18.4) | 68 (20.7) | |
| T3 | 424 (45.5) | 126 (44.4) | 153 (47.8) | 145 (44.2) | |
| T4 | 49 (5.3) | 18 (6.3) | 14 (4.4) | 17 (5.2) | |
| TNM n (%) | | | | | 0.526 |
| I | 401 (43.0) | 120 (42.3) | 139 (43.4) | 142 (43.3) | |
| II | 481 (51.6) | 146 (51.4) | 167 (52.2) | 168 (51.2) | |
| III | 47 (5.0) | 18 (6.3) | 14 (4.4) | 15 (4.6) | |
| IV | 3 (0.3) | 0 (0) | 0 (0) | 3 (0.9) | |
| Chemotherapy n (%) | | | | | 0.182 |
| No | 362 (38.8) | 110 (38.7) | 113 (35.3) | 139 (42.4) | |
| Yes | 570 (61.2) | 174 (61.3) | 207 (64.7) | 189 (57.6) | |
| Radiotherapy, n (%) | | | | | 0.084 |
| No | 379 (40.7) | 114 (40.1) | 117 (36.6) | 148 (45.1) | |
| Yes | 553 (59.3) | 170 (59.9) | 203 (63.4) | 180 (54.9) | |
| Follow-up time | 44.6 ± 39.3 | 42.8 ± 41.1 | 46.1 ± 39.3 | 44.8 ± 37.5 | 0.57 |
| Survival Status n (%) | | | | | < 0.001 |
| Alive | 423 (45.4) | 96 (33.8) | 152 (47.5) | 175 (53.4) | |
| Dead | 509 (54.6) | 188 (66.2) | 168 (52.5) | 153 (46.6) | |

race, T stage, TNM, location, grade, chemotherapy, and radiotherapy was 0.98 [(0.97, 0.99) $p$ = 0.005]. The significance was not clearly evident in the Taizhou Hospital data, which could be attributed to the limited sample size.

The stratified analyses of the associations between the number of resected LNs and survival status in node-negative ESCC are presented in Figures 3 and 4. In SEER a significant interaction was observed for the radiotherapy variable (HR 0.98 (0.97–0.99)) and chemotherapy variable (HR 0.98 (0.97–0.99)). No significant interactions were found for the other variables, including age, gender, race, location, TNM,(Figure 3). In TaiZhou hospital database We did not find any interaction between the number of resected LNs and age, gender for female, Location, survival status in node-negative ESCC after surgical treatment. Nevertheless, the association of the number of resected LNs and survival status in node-negative ESCC after surgical treatment was stronger among TNM system II (HR 1.09 (1.03–1.21)), gender for male (HR 1.07 (1.01–1.41)), Chemoradiotherapy (HR 1.07 (1.01–1.15)).(Figure 4).

**Table 2** Baseline Characteristics of Patients in TaiZhou Hospital

| Variables | Total (n = 67) | Q1 (n = 20) | Q2(n = 22) | Q3 (n = 25) | p |
|---|---|---|---|---|---|
| Age (Mean ± SD) | 66.4 ± 6.3 | 68.2 ± 5.6 | 67.9 ± 7.6 | 63.8 ± 4.7 | 0.025 |
| Gender, n (%) | | | | | 0.302 |
| Male | 44 (65.7) | 13 (65) | 12 (54.5) | 19 (76) | |
| Female | 23 (34.3) | 7 (35) | 10 (45.5) | 6 (24) | |
| Location, n (%) | | | | | 0.383 |
| Up | 9 (13.4) | 2 (10) | 4 (18.2) | 3 (12) | |
| Middle | 35 (52.2) | 10 (50) | 14 (63.6) | 11 (44) | |
| Low | 23 (34.3) | 8 (40) | 4 (18.2) | 11 (44) | |
| Grade n (%) | | | | | 0.541 |
| Low | 13 (19.4) | 5 (25) | 5 (22.7) | 3 (12) | |
| Middle | 42 (62.7) | 11 (55) | 15 (68.2) | 16 (64) | |
| High | 12 (17.9) | 4 (20) | 2 (9.1) | 6 (24) | |
| Stage T n (%) | | | | | 0.623 |
| T1 | 22 (32.8) | 8 (40) | 8 (36.4) | 6 (24) | |
| T2 | 14 (20.9) | 5 (25) | 3 (13.6) | 6 (24) | |
| T3 | 31 (46.3) | 7 (35) | 11 (50) | 13 (52) | |
| TNM n (%) | | | | | 0.496 |
| I | 24 (35.8) | 9 (45) | 8 (36.4) | 7 (28) | |
| II | 43 (64.2) | 11 (55) | 14 (63.6) | 18 (72) | |
| Chemoradiotherapy n (%) | | | | | 0.857 |
| No | 49 (73.1) | 14 (70) | 17 (77.3) | 18 (72) | |
| Yes | 18 (26.9) | 6 (30) | 5 (22.7) | 7 (28) | |
| Follow-up time | 13.8 (8.6, 22.8) | 19.0(11.2,25.6) | 13.6(6.4,21.9) | 13.2(5.0,17.2) | 0.101 |
| Survival Status n (%) | | | | | 0.854 |
| Alive | 62 (92.5) | 18 (90) | 21 (95.5) | 23 (92) | |
| Death | 5 (7.5) | 2 (10) | 1 (4.5) | 2 (8) | |

## Discussion

According to the findings of this study, restricted cubic spline regression was used to determine whether there is a nonlinear relationship between the number of resected lymph nodes and survival status in node-negative esophageal squamous cell carcinoma. There was an incremental improvement in survival along with the increase in the number of resected lymph nodes, and the optimal number appears to be 25 ~28 or more.

There are numerous factors determining the prognosis for EC. In the National Comprehensive Cancer Network (NCCN) guidelines, the tumor, node, metastasis (TNM) system is used to stage EC and describe the depth of tumor invasion, lymph node status, tumor location, tumor differentiation degree, and tumor response to combined therapy. In addition to clinical (c) and pathologic (p) stages, other prognostic factors are patient age, sex, and surgical method. With the development of technology, the operative mortality rate for esophagectomy has been markedly reduced. Currently, lymph node detection and dissection have received considerable scholarly attention toward improving the prognosis for EC.

Given that opinions differ as to the minimum number of LNs that should be resected during esophagectomy, a protocol for LNR should be established to guide treatment for patients with EC.[8,9] In a retrospective monocentric study, Chinese researchers suggested that in operable cases, resection of 18 LNs allows accurate staging and optimal treatment of EC, and the LN-negative group demonstrated a significant increase in the overall survival rate.[10] While some researchers note that resection of 13–29 LNs is associated with a higher survival rate, others have found no clear relationship between the number of resected LNs and the survival rate of patients receiving neoadjuvant therapy.[11] Rizk et al[12] discovered that in LN-positive cases, optimal LNR requires at least 10 LNs for pT1, 20 for pT2, and 30 for pT3/T4; in LN-negative cases, the optimum is at least 10–12 LNs for pT1, 15–22 for pT2, and 31–42 for pT3/T4. These findings have been accepted by the NCCN and included in the guidelines. Torgersen et al[13] found that the extent of LNR

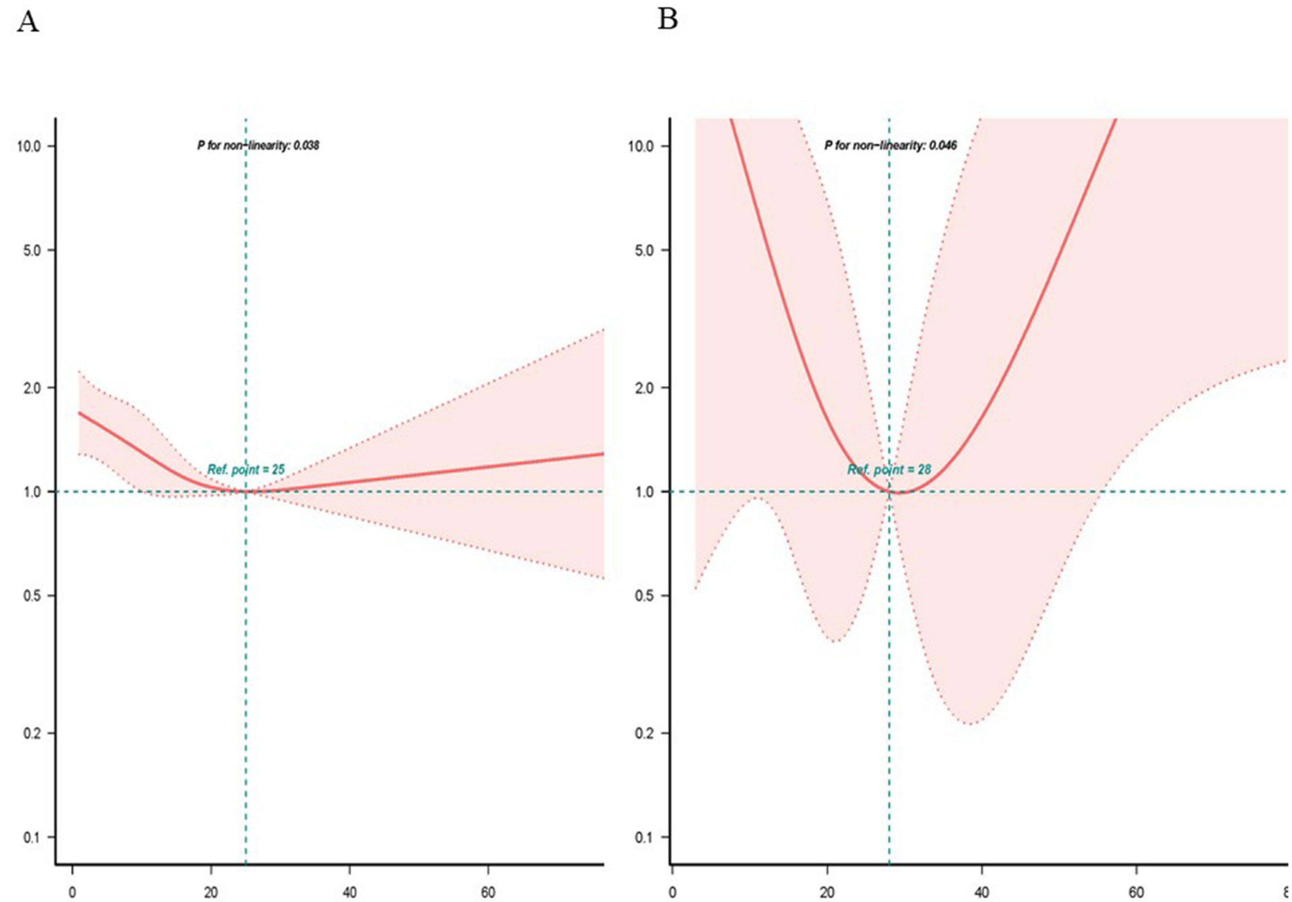


**Figure 2** The relationship for the number of lymph node resections with survival status in node-negative esophageal squamous cell carcinoma. (**A**) Restricted cubic spline for survival status of patients in SEER. (**B**) Restricted cubic spline for survival status of patients in TaiZhou hospital.

and the ratio of positive to total lymph nodes are two important prognostic factors for esophagectomy post-neoadjuvant therapy, and resection of ≥18 LNs is associated with a significantly higher survival rate. Another retrospective analysis involving 1399 patients who had received neoadjuvant chemoradiotherapy (CRT) plus surgical treatments revealed that the total number of resected LNs is linked to the survival rate of patients receiving esophagectomy after neoadjuvant CRT, with resection of >20 LNs producing a better prognosis than that of ≤21 LNs.[14] A meta-analysis of 26 studies compared the effects of LNR on survival in patients receiving and not receiving neoadjuvant therapy for EC and

**Table 3** Relationship Between Resected Lymph Node Number and Survival Status in Node-Negative Esophageal

| Variable | Model I | | Model II | | Model III | |
|---|---|---|---|---|---|---|
| | (HR,95% CI) | P-value | (HR,95% CI) | P-value | (HR,95% CI) | P-value |
| LNs of SEER | 0.987(0.979, 0.996) | 0.0044 | 0.986 (0.977, 0.995) | 0.0019 | 0.987 (0.978, 0.996) | 0.0058 |
| T1 | Ref | | Ref | | Ref | |
| T2 | 0.742 (0.602~0.913) | 0.0049 | 0.756 (0.614~0.932) | 0.0087 | 0.734 (0.595~0.906) | 0.0039 |
| T3 | 0.663 (0.536~0.821) | 0.0002 | 0.646 (0.521~0.800) | 0.0001 | 0.670(0.538~0.835) | 0.0004 |
| LNs of TaiZhou | 1.03(0.97, 1.09) | 0.266 | 1.03(0.97, 1.08) | 0.376 | 1.03(0.96, 1.11) | 0.474 |
| Q1 | (Ref) | | (Ref) | | (Ref) | |
| Q2 | 0.98(0.09, 7.50) | 0.988 | 0.82(0.07, 6.62) | 0.856 | 1.08(0.06, 19.73) | 0.961 |
| Q3 | 1.54(0.23, 10.40) | 0.641 | 1.08(0.16, 7.57) | 0.935 | 1.37(0.09, 21.69) | 0.823 |

**Note**: Model I, not adjusted. Model II: we adjust age and gender. Model III: we adjust age, sex, race, T stage, TNM, location, grade, chemotherapy, radiotherapy.

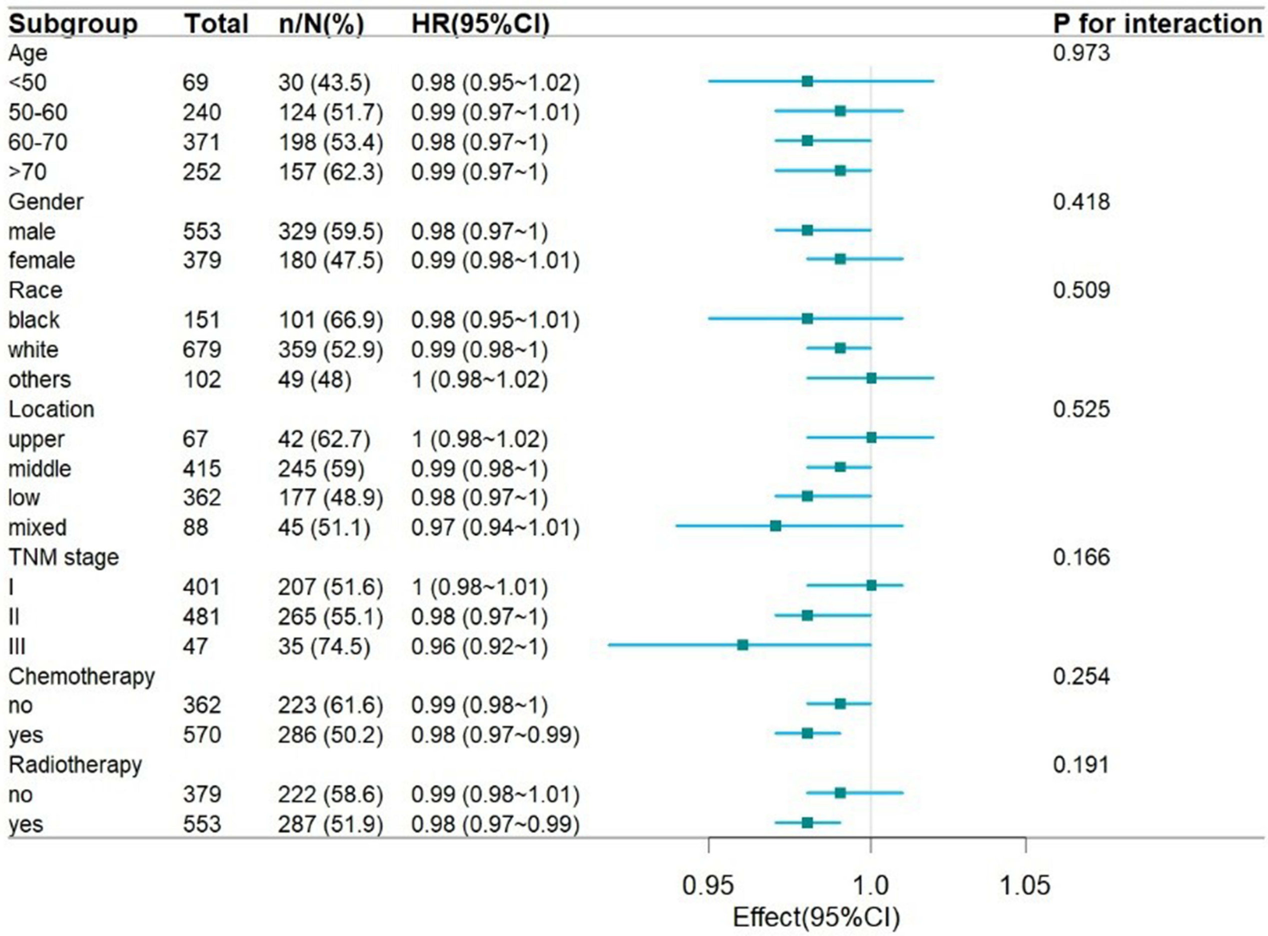


**Figure 3** Estimated HR for the prognosis of patients with node-negative ESCC in SEER.

concluded that a greater number of resected LNs means better long-term survival regardless of the use of neoadjuvant therapy.[15] While the debate continues about the ideal number of LNs to be resected in patients with EC, researchers have not yet come up with any convincing evidence. The NCCN guidelines suggest the preoperative removal of at least 15 LNs in patients with EC.

Recent studies on ESCC have demonstrated that the impact of lymph node dissection varies significantly before and after neoadjuvant therapy, with the status of the lymph nodes (positive or negative) further influencing outcomes. A systemic lymphadenectomy should still be considered as an integrated part of surgery.[16] Some degree of lymphadenectomy after neoadjuvant chemotherapy (NCT) was beneficial in improving 5-year OS and DFS for ESCC patients with nodal metastases. For patients with nodal negativity, more extended lymphadenectomy did not improve patient survival.[17] Increasing the number of LNs harvested during surgery to 24 or more could improve the OS of patients with positive LNs but not that of patients with negative LNs.[18] Additionally, The number of stations from which lymph nodes are resected is as critical as the total number of nodes removed. In a recent study by Lu et al,[19] the impact of the extent of lymph node dissection (LND) on the survival of patients with esophageal squamous cell carcinoma (ESCC) who underwent neoadjuvant chemoradiotherapy (nCRT) was investigated. The research analyzed a cohort of 333 patients and found that a higher number of lymph node stations dissected (e-LNS) was significantly associated with improved overall survival (OS) and disease-free survival (DFS). A study by K. Li et al[20] specifically examines the impact of the number of metastatic lymph nodes on overall survival (OS), using propensity score-matching (PSM) to adjust for confounding variables and ensure comparability between groups. The study's findings suggest that patients with a single metastatic lymph node (Group 1) have a significantly longer median OS compared to those with two metastatic lymph

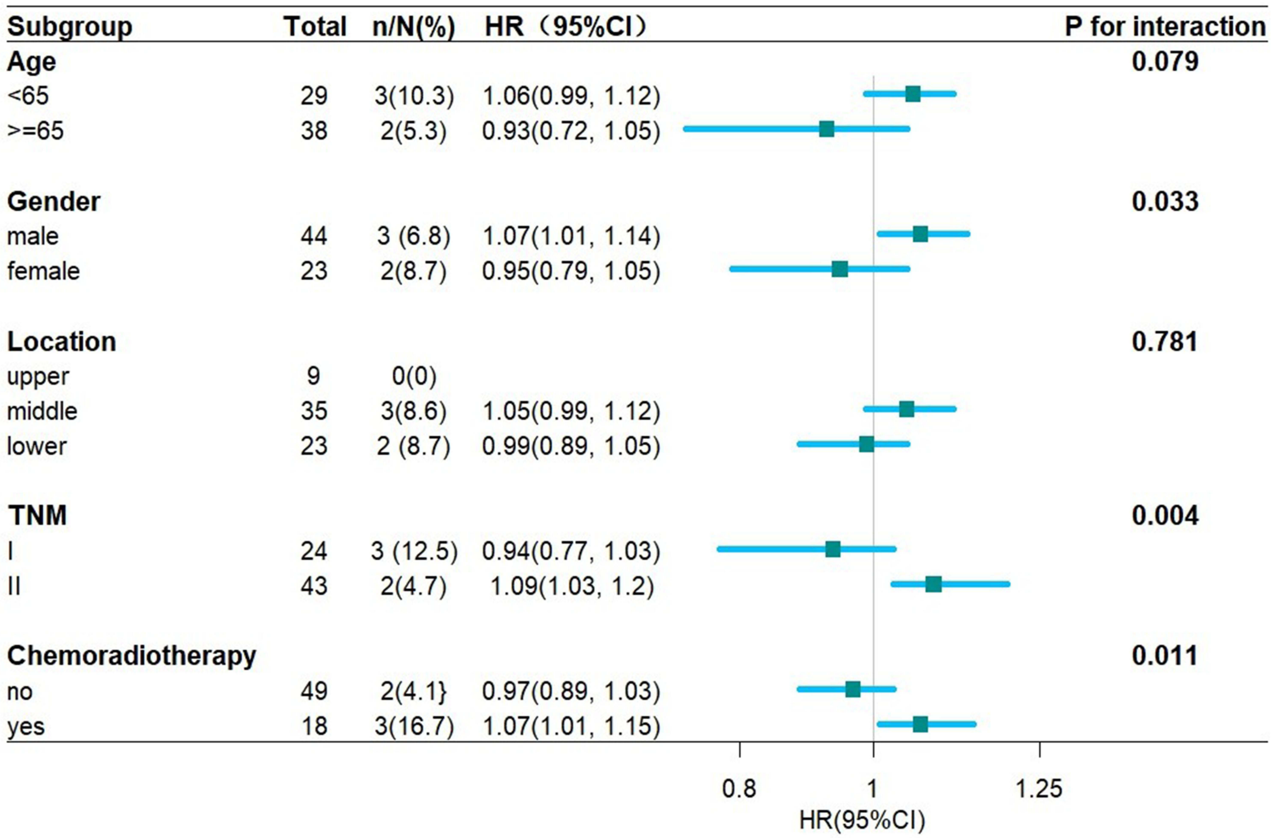


**Figure 4** Estimated HR for the prognosis of patients with node-negative ESCC in TaiZhou hospital.

nodes (Group 2), highlighting the prognostic significance of lymph node involvement in ESCC. A study from China discusses the impact of lymph node station location on survival in esophageal squamous cell carcinoma (ESCC) patients with pN1 disease which analyzed 807 patients and found that the number and spread of metastatic lymph nodes across different stations significantly affect survival and suggests that lymphadenectomy may still be therapeutic after neoadjuvant therapies.[21] ESCC has a unique lymphatic drainage pattern, resulting in varying rates of metastasis across different lymph node stations. Tachimori et al[22] demonstrated that the efficacy of lymph node dissection varies by tumor location in esophageal squamous cell carcinoma, emphasizing the importance of tailored surgical approaches based on tumor-specific characteristics. In a study by Koenig et al[23] the impact of micrometastatic tumor cell load in patients with esophageal carcinoma was examined. The findings indicated that even a minimal tumor cell load, as assessed by the ratio of micrometastatically affected lymph nodes, can serve as a complementary tool for better risk stratification of these patients.

Moreover, the degree of lymph node response in different regions post-neoadjuvant therapy can vary significantly, One-third of the patients who have undergone R0 resection for esophageal adenocarcinoma following induction chemoradiation therapy have metastatic lymph nodes.[24] N stage remains the optimum predictor of prognosis for ESCC patients after NCT and surgery.[25]

Generally, pN0 cases have a significantly better prognosis than pN+ cases. However, the pathological diagnosis of N0 EC needs further confirmation by adequate LNR. Considering the usually unsatisfactory detection of regional lymph node metastasis in EC, in most cases, it is difficult to eliminate all metastatic LNs within a given operation time. Notably, a prolonged operation is associated with increased intra- and post-operative risks. This denotes the practical significance of defining the ideal number of LNs to be resected in patients with EC, which provides helpful guidance on the choice of surgical approaches.

Studies by Yang et al and Greenstein et al[10,26] found that the resection of 18 LNs can improve the survival of patients with pN0 EC. However, these findings have not been further validated in patients with ESCC. By comparing 666 patients with pN0 ESCC who were assigned to three different groups subject to resection of <9, 10–15, and ≥16 LNs, Liu et al[27] noted a remarkable improvement in the long-term survival of patients who underwent removal of ≥16 LNs. Evidence shows that resection of ≥9 LNs can produce a higher survival rate in patients with pN0M0 thoracic ESCC.

Existing literature indicates a link between the LN-positive rate and the post-operative long-term survival rate. However, excessive LNR is associated with decreased survival benefits.[28,29] A randomized controlled trial[30] reported that there is no significant difference in short- or long-term survival between patients receiving two-field and three-field LNR. Collectively, determining the minimum number of LNs that should be removed in EC cases is essential for the planning of further treatment and follow-up strategies. More effort is needed to develop a feasible survival prognostic model, thereby delivering improved precision treatment options to patients with LN-negative ESCC post-operative.

This study has some limitations. First, the retrospective design is intrinsically biased. Second, patients receiving different modalities of neoadjuvant therapy were not studied separately because the database does not specify neoadjuvant therapy, such as radiotherapy, chemotherapy, and CRT. Third, minimally invasive surgery, albeit with its emerging application in the field, has not been distinguished from open surgery. Fourth, When comparing the SEER and Taizhou hospital datasets, we observed some differences that may stem from variations in population characteristics. The SEER dataset primarily includes populations from North America, while the Taizhou hospital dataset is more region-specific, reflecting the characteristics of the population in Eastern China. Fifth, differences in medical standards could be a significant factor, potentially leading to variations in the optimal number of lymph nodes and influencing the research outcomes. To address this, we employed Firth's penalization to correct the partial likelihood within the analysis of the Taizhou hospital cohort. Lastly, larger-scale prospective clinical studies, including multicenter randomized controlled trials, are needed to examine the impact of lymph node dissection on the survival of esophageal cancer patients. Such studies will help determine the optimal number of lymph nodes to be dissected and develop more comprehensive dissection strategies to guide the multidisciplinary treatment of esophageal cancer.

## Conclusion

In summary, we found that lymph node resection conferred a survival benefit for patients with node-negative ESCC and a low count of resected lymph nodes was associated with a decreased survival benefit. Survival benefit Increased with an increasing number of resected lymph nodes until 25~28 nodes. Clinical trials are needed to determine the potential effects of Number of Resected LNs and Survival Status in Node-negative ESCC.

## Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethical Approval

The study was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province, which is affiliated with Wenzhou Medical University. The approval number for this study is L2024-01-63-01. All procedures were performed in accordance with the guidelines set by the committee. The Ethics Committee of Taizhou Hospital waived the requirement for patient consent to review their medical records due to the retrospective nature of the study. Patient data confidentiality was strictly maintained, and all data were anonymized and handled in compliance with the Declaration of Helsinki.

## Author Contributions

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

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## Disclosure

The authors report no conflicts of interest in this work.

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