Characteristics And Prognostic Value of Lymph Node Metastasis Along Recurrent Laryngeal Nerves in Thoracic Esophageal Squamous Cell Carcinoma

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Research Article

Keywords: Esophageal squamous cell carcinoma, Recurrent laryngeal nerve, Lymph node metastasis, survival

Posted Date: October 5th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-927022/v1

Abstract

Background: Though the value of lymph node (LN) dissection along bilateral recurrent laryngeal nerve (RLN) has been debated and emphasized in recent years in thoracic esophageal squamous cell carcinoma (ESCC). However, the characteristics of nodal metastasis along RLN chain has not been clarified. This study aimed to investigate the characteristics of nodal metastasis along recurrent laryngeal nerves and the influence of these metastasis on the prognosis of thoracic ESCC.

Patients and Methods: 339 eligible patients with thoracic ESCC who underwent esophagectomy with a three-field(3-FL) or two-field(2-FL) lymph node dissection from March 2015 to December 2018 were included in this study, consisting of 282 males and 57 females with a mean age of 60.6 years (range,40-80 years). The association of LN metastasis near RLN with clinicopathologic factors and its influence on survival were analyzed.

Results: Among the 339 patients, 96 (28.3%) had LN metastasis along bilateral recurrent laryngeal nerves, 76 (22.4%) with positive LNs along right RLN and 47 (13.9%) along the left RLN. There was a significant difference in the metastasis rate between the LNs along right RLN and along the left RLN (P=0.004). The LN metastasis rate along RLN was significantly correlated with primary tumor locations (upper vs middle vs lower: 35.1% vs 30.9% vs 15.6%; P=0.015), tumor invasion depth (T3/T4 vs T1 vs T2: 36.2% vs 15.8% vs 26.2%, P=0.001) and degree of differentiation (well vs moderately vs poorly: 9.3% vs 29.3% vs 33.9%; P=0.009), subcarinal and left tracheobronchial lymph node metastasis (positive vs negative:58.1% vs 25.3%, P0.001), abdominal LN metastasis (positive vs negative:41.2% vs 24.0%, P=0.003), but was not significantly correlated with age, gender and tumor length. The median follow-up time for this study was 34 months. The cumulative 1-, 2- and 3-year overall survival rates were 95.7%, 86.6% and 82.2% in RLN-LN(-) group versus 81.5%, 67.4% and 53.7% in the RLN-LN(+) group, with a significant difference between two group (HR=2.975,95% CI:1.918-4.614, P0.01).

Conclusions: The lymph node metastasis along RLNs was significantly correlated with primary tumor locations, tumor invasion depth, tumor differentiation, metastasis in the LNs of other stations, and indicate poor prognosis in ESCC.

Background

Lymph node (LN) metastasis has been reported as a significant prognostic factor in the patients with thoracic esophageal squamous cell carcinoma (ESCC) [1]. Cancer cells of the thoracic ESCC could spread widely to the cervical and abdominal lymph nodes besides mediastinal lymph nodes through rich longitudinal lymphoid vessels in the submucosa of the esophagus, and this usually leads to poor prognosis [2]. LNs near recurrent laryngeal nerve were reported as the most common sites of nodal metastasis of ESCC in the chest [3], and metastasis to these nodes usually indicated poor prognosis. Historically, lymph node dissection (LND) along the recurrent laryngeal nerve chain has not been emphasized in China during the past decades because most patients with ESCC underwent

esophagectomies through left thoracotomy instead of right thoracic approach. This leads to frequent recurrence in the cervicothoracic area, which was just the recurrences from the LN metastasis along RLN chain [4]. In recent years, as the video-assisted thoracic surgery (VATS) getting its popularity across China, LND along RLNs has been emphasized gradually and performed in the patients with thoracic ESCC as a standardized procedure in most hospitals [5]. However, the advantages and disadvantages of LND along RLN chain have not been fully clarified either [6]. Therefore, in order to clarify these factors, we retrospectively analyzed the association of LN metastasis along RLNs with clinicopathologic factors, and its influence on the overall survival in the thoracic ESCC patients who underwent 2-field or 3-field lymph node dissection via right thoracic approach in our center during the past years.

Methods

Patient enrollment:

Inclusion criteria

From March 2015 to December 2018, totally, 1686 hospitalized patients with resectable thoracic ESCC underwent esophagectomy in our hospital. The patients were selected into this study according to the following criteria: (1) R0 resection; (2) pathologically confirmed squamous cell carcinoma; (3) with 2FL or 3FL LN dissection including LNs along bilateral recurrent laryngeal nerves; (4) preoperative clinical TNM stage within cT1b-3N0-1M0; (5) resection through right thoracic approach; (6) without preoperative suspected distant metastasis. (7) without simultaneous or past other malignant tumors; (8) without neoadjuvant anti-cancer therapy. Finally, 339 eligible patients were selected into this study (Fig. 1).

High resolution and enhanced chest/abdominal CT scans, bone scanning, brain MRI/CT, neck ultrasonography; FOE and EUS were performed preoperatively in all patients in order to exclude distant metastasis and make a precise clinical TNM staging. All specimens were examined pathologically at the Department of Pathology in our institution. The seventh edition UICC esophageal cancer staging criteria was used for pathological TNM classification. The ethic approval was waived by Ethic Committee of National Cancer Center of China after submitting the study protocol and discussion.

Principle Surgical Procedure

All 339 patients underwent McKeown or Ivor-Lewis esophagectomy via either open procedures through conventional three incisions (thoracotomy + midline laparotomy + left neck incision) or minimally invasive procedures (thoracoscopy/laparoscopy + neck incision). Lymph nodes in the chest including periesophageal lymph nodes, bilateral recurrent laryngeal nerve lymph nodes, subcarinal lymph nodes, and left tracheobronchial lymph nodes were all dissected. The abdominal lymph nodes consisting of paracardial, lesser curvature, and left gastric artery, splenic artery, common hepatic artery were all

dissected. Next, the stomach conduit was made and pulled to the neck or the apex of the right thorax through esophageal bed, a handsewn or stapled gastro-esophageal anastomosis was carried out.

Statistical analysis

All statistical analysis was performed using IBM SPSS Statistics ver. 22.0(SPSS Inc, Chicago, IL, USA). Chi-square test or Fisher's exact test was used to compare categorical data. Student's t test was used for continuous data. OS was created using the Kaplan-Meier method and compared between two groups using log-rank test. Univariate Cox regression analysis was used to estimate the hazard ratios of OS. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

The clinical and pathologic characteristics of the study population are summarized in Table 1. There were 282 men and 57 women with a mean age of 60.6 years, (range: 40-80 years). Of the 339 patients, 74 had tumors located at the upper third esophagus, 188 at the middle third, 77 at the lower third. All 339 patients underwent either McKeown (325) or Ivor-Lewis (14) esophagectomy by open or MIE procedure through right thoracic approach. 75 underwent 3-FL LND, and the other 264 received 2-FL LND.

Table 1
Clinical and Pathologic characteristics of 339 patients

Characteristics	Number of Patients(percentage)
Total cases	339
Mean age(range)	60.6 (range: 40-80 years)
Sex	
Male	282(83.2%)
Female	57(16.8%)
Tumor location	
Upper	74(21.8%)
Middle	188(55.5%)
Lower	77(22.7%)
Tumor differentiation	
Well	43(12.7%)
Moderate	181(53.4%)
Poor	115(33.9%)
T Classification	
T1	101(29.8%)
T2	61(18.0%)
T3	160(47.2%)
T4	17(5.0%)
M classification	
M0	339(100%)
Range of lymph node dissection	
2-FL	264(77.9%)
3-FL	75(22.1%)
Anastomotic methods	
Handsewn	187(55.2%)
Stapled	152(44.8%)
Anastomosis location	

Characteristics	Number of Patients(percentage)
Thoracic	14(4.1%)
Cervical	325(95.9%)
pTNMstage	
IA	14(4.1%)
IB	64(18.9%)
IIA	31(9.1%)
IIB	93(27.4%)
IIIA	64(18.9%)
IIIB	40(11.8%)
IIIC	33(9.7%)

Characteristics of LN metastasis in the chest

Among the 339 patients, a total of 2279 LNs along recurrent laryngeal nerve were dissected, with a mean dissected LNs of 6.7; 186 metastatic LNs were detected with a metastasis ratio of 8.2%. Of the 339 patients, 96 (28.3%) had LN metastasis along recurrent laryngeal nerves. The LN metastasis rate of the right and left RLN-LNs was 22.4% and 13.9%, respectively, there was a significant difference between the right RLN-LNs and left RLN-LNs (P=0.004). The metastasis rate of subcarinal and left tracheobronchial LNs, upper periesophageal LNs, middle periesophageal LNs and lower periesophageal LNs was 9.1%, 5.0%, 7.1% and 8.8%, respectively.

Correlation of LN metastasis along RLNs with clinicopathological factors

The correlations of LN metastasis along RLNs with clinicopathological factors were summarized in the Table 2. Univariate analysis showed that the LNs metastasis rate of RLN was significantly correlated with the tumor locations, tumor invasion depth, tumor differentiation and the LN metastasis of other stations in the chest and abdomen.

The LN metastasis rate of RLNs in the patients with upper thoracic esophageal cancers was 35.1%, which was significantly higher than that in the patients with middle (30.9%) and lower (15.6%) thoracic esophageal cancers (P=0.015). The LN metastasis rate of RLNs was significantly higher in the patients with T3/T4 esophageal cancers (36.2%) than that in the patients with T1 (15.8%) and T2 (26.2%) tumors, (P=0.001). The LN metastasis rate of RLNs in the patients with well, moderately and poorly differentiated

tumors were 9.3%, 29.3% and 33.9%, respectively, there was significant difference among three groups(P=0.009). The LN metastasis rate of RLNs in the patients with positive subcarinal lymph nodes /left tracheobronchial lymph nodes, was significantly higher than that in the patients with negative LNs (58.1% vs 25.3%, P<0.001), furthermore, it was also significantly higher in the patients with positive abdominal LNs than that in the patients with negative LNs(41.2% vs 24.0%, P=0.003).

Table 2
Correlations of clinical characteristics with LN metastasis along RLNs

Characteristics	Category	RLN-LNs(+) (n=96)	RLN-LNs(-) (n=243)	Rate of metastatic RLN-LNs	*P*-value
Gender					
	Male	85	197	30.1%	0.11
	Female	11	46	19.30%	
Age(years)					
	≤60	44	112	28.2%	1
	60	52	131	28.4%	
Tumor length					
	≤5cm	34	86	28.3%	1
	5cm	62	157	28.3%	
T Classification					
	T1	16	85	15.8%	0.001
	T2	16	45	26.2%	
	T3+T4	64	113	36.2%	
Tumor differentiation					
	Well	4	39	9.3%	0.009
	Moderate	53	128	29.3%	
	Poor	39	76	33.9%	
Primary tumor location					
	Upper	26	48	35.1%	0.015
	Middle	58	130	30.9%	

LN: lymph node
RLN: recurrent laryngeal nerve

RLN-LNs: lymph nodes of recurrent laryngeal nerves

RLN-LNs(+): Positive metastatic lymph nodes of recurrent laryngeal nerves

RLN-LNs(-): negative metastatic lymph nodes of recurrent laryngeal nerves

Characteristics	Category	RLN-LNs(+) (n=96)	RLN-LNs(-) (n=243)	Rate of metastatic RLN-LNs	*P*-value
	Lower	12	65	15.6%	
Left tracheobronchial and subcarinal LN					
	Positive	18	13	58.1%	0.001
	Negative	78	230	25.3%	
Abdominal LN					
	Positive	35	50	41.2%	0.003
	Negative	61	193	24.0%	

LN: lymph node
RLN: recurrent laryngeal nerve

RLN-LNs: lymph nodes of recurrent laryngeal nerves

RLN-LNs(+): Positive metastatic lymph nodes of recurrent laryngeal nerves

RLN-LNs(-): negative metastatic lymph nodes of recurrent laryngeal nerves

Correlation between LN metastasis along RLNs and Survival

By the end of March 31, 2021, the median follow-up time for surviving was 34 months (range: 6-72). A total of 15 patients (4.4%) were lost to follow-up, including 11(4.5%) in RLN-LNs(-) group and 4(4.1%) in RLN-LNs(+) group. Of the 339 patients, 244 (75.3%) patients were still alive at the time of this analysis. A total of 80 (24.7%) have been dead within the period of study.

Three patients (0.9%) died of respiratory failure within 90 days postoperatively. The cumulative OS rates at 1-, 2- and 3-year were 95.7%,86.6% and 82.2% in the RLN-LNs(-) group versus 81.5%, 67.4%, and53.7% in the RLN-LNs(+) group (HR=2.975,95% CI:1.918-4.614, P 0.01)(Fig. 2). The cumulative DFS rates at 1-, 2- and 3-year were 84.5%,74.5% and 71.8% in RLN-LNs(-) group versus 70.7%, 48.9% and 43.1% in RLN-LNs(+) group(HR 2.421, 95% CI:1.679-3.489, P 0.01) (Fig. 3). The 1-, 2-, and 3-year survival rate of the 51 patients with single metastatic RLN LN was 90.2%, 76.5% and 58% versus 73.2%, 53.7% and 48.2% of the 41 patients with more than 2 metastatic RLN-LNs (HR 1.725, 95% CI 0.926-3.214, P=0.086). The 1-, 2-, and 3-year cumulative OS in the patients with metastasis in the other LN stations was remarkably higher than that in the patients with metastasis of RLN-LNs, but there was no significant difference between two groups (HR1.356,95%CI 0.812-2.265, P=0.245) (Fig. 4). Besides, cumulative OS in patients without any LNs metastasis was significantly higher than that in patients with only RLN LN metastasis (HR 2.841,95%CI 1.33-6.069, P=0.007) (Fig. 5). Compared to patients without any LNs metastasis and

patients with only RLN LNs, OS of patients with RLN LNs and other LNs metastasis was significantly poorer (Fig. 6)

Discussion

The esophageal submucosa is rich in vertical and horizontal lymphatic vessels, which communicates with each other in the esophagus and in the mediastinal lymph network. Once tumor invades the submucosal layer, the tumor cells can spread along the longitudinal lymphatic vessels in the esophageal submucosa to the remote LNs, which result in distant or skip metastasis [5]. LN metastasis in the upper mediastinum and cervical region is the main cause of local recurrence of esophageal cancer in the thoracic esophageal cancer [7]. LN metastasis along bilateral RLN was reported to account for a major proportion of the mediastina LNs. Fujita et al. reported that the LN metastasis rate along right recurrent laryngeal nerve was the highest among all LN stations around the esophagus [3]. Ye et al. reported that the LN metastasis rate along the bilateral recurrent laryngeal nerves was 34.2% in total, 15.8% for the left RLN and 20.8% for the right RLN [8–9]. In our study, the LN metastasis rate along bilateral RLNs was 28.3%, which was much higher than that in the other mediastinal lymph node stations. Our result is consistent with what has been reported in the literatures [10–13]. Furthermore, it was 22.4% for the nodes along the right RLN and 13.9% along the left RLN, with a significant difference between the right and left RLN (P=0.004). This suggests esophageal cancer has a predilection of metastasis to the nodes along bilateral RLNs, while the LNs along right RLN are the most common metastasis station. Therefore, LNs dissection along bilateral RLN is a necessary procedure in the patients with thoracic ESCC, which not only increase accuracy of tumor staging, but also improve R0 resection.

In this study, it was found that LN metastasis rate along bilateral RLNs was significantly correlated with primary tumor sites, tumor differentiation and depth of tumor invasion in the patients with thoracic ESCC, this is consistent with the results reported in the literatures [9–11]. Upper third thoracic esophageal tumors, T3/T4 tumors and poorly differentiated tumors have much higher risk of LN metastasis along RLNs, and deserve more extensive LN dissection. It was reported that lower third thoracic ESCC mainly metastasize downward to the LNs around paracardia and left gastric artery. However, our study showed that the lower third thoracic ESCC also had a high LN metastasis rate along RLNs. This implies that complete LN dissection near bilateral RLNs should also be emphasized as a necessary procedure in those patients. Our study also found that the LN metastasis rate along RLNs was significantly higher in the patients with the positive LNs of other stations such as subcarinal, left tracheobronchial and upper abdominal stations than those with negative LNs in the other stations. This suggest that more advanced stage tumors have much higher risk of LNs metastasis along RLNs.

It has been reported that LN metastasis was one of the most important factors affecting the prognosis of patients with esophageal cancer. Not only the number of metastatic LNs, but also the site of LN metastasis, particularly the RLN-LNs, was an important prognostic indicator [13]. Our study demonstrated that the OS and DFS of the patients with LN metastasis along RLNs were significantly poorer than that of those without and those with LN metastasis in other stations. Therefore, the LN metastasis along RLNs

usually indicated an advanced stage. Another interesting finding was that the prognosis of the patients with single RLN nodal metastasis was much better than the patients with ≥2 nodal metastasis. All the above findings suggested that LN metastasis along RLNs was an important prognostic factor for the patients with thoracic ESCC, and neoadjuvant therapy may be necessary for those patients with preoperative suspicious nodal metastasis along RLNs.

Besides, RLNP occurred in 38 patients (11.2%). The incidence of RLNP was related to the degree of lymph node dissection (3FL 24.0% versus 2FL 7.6%, P<0.001), and was not related to operation method, tumor T stage, and degree of tumor differentiation (P>0.05).

The limitation of this study is that this was a retrospective study, and all included patients were from a single center and operated by a group of surgeons with difference in surgical skills and experience, which may produce bias in the results. And this study lacks data on postoperative treatment of the included patients and the impact of postoperative treatment on survival was missing. Besides, factors cause the higher metastasis rate of the right RLN chain lymph node were also not explained in our study.

In conclusion, for the patients with thoracic ESCC, RLN-LNs are the most frequent metastatic sites; the metastasis in the RLN-LNs significantly correlated with tumor invasion depth, tumor locations and differentiation, and usually indicate an advanced stage and poor prognosis. Complete LN dissection of bilateral RLNs is strongly recommend for the patients with thoracic ESCC.

Abbreviations

LN, lymph node; RLN, recurrent laryngeal nerve; ESCC, esophageal squamous cell carcinoma; LND, lymph node dissection; VATS, video-assisted thoracic surgery; RLN-LNs, lymph nodes of recurrent laryngeal nerves; RLN-LNs(+), Positive metastatic lymph nodes of recurrent laryngeal nerves; RLN-LNs(-), negative metastatic lymph nodes of recurrent laryngeal nerves; CI, confidence interval; OS, Overall survival; HR, hazard ratio; DFS, disease-free survival.

Declarations

Acknowledgements:

Thanks to all participants who have made contribution to our work.

Ethics approval and consent to participate:

The study was independently approved by the Ethics committee of Cancer Hospital Chinese Academy of Medical Sciences (Approval No.15-032/959). All procedures performed in this study were conducted

following the Declaration of Helsinki (as revised in 2013). All patients provided written informed consent before enrollment.

Consent for publication:

Yes

Availability of data and material:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Funding:

None

Authors' contributions:

Ligong Yuan wrote the main manuscript text and Feng Li prepared figures. All authors reviewed the manuscript.

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Figures

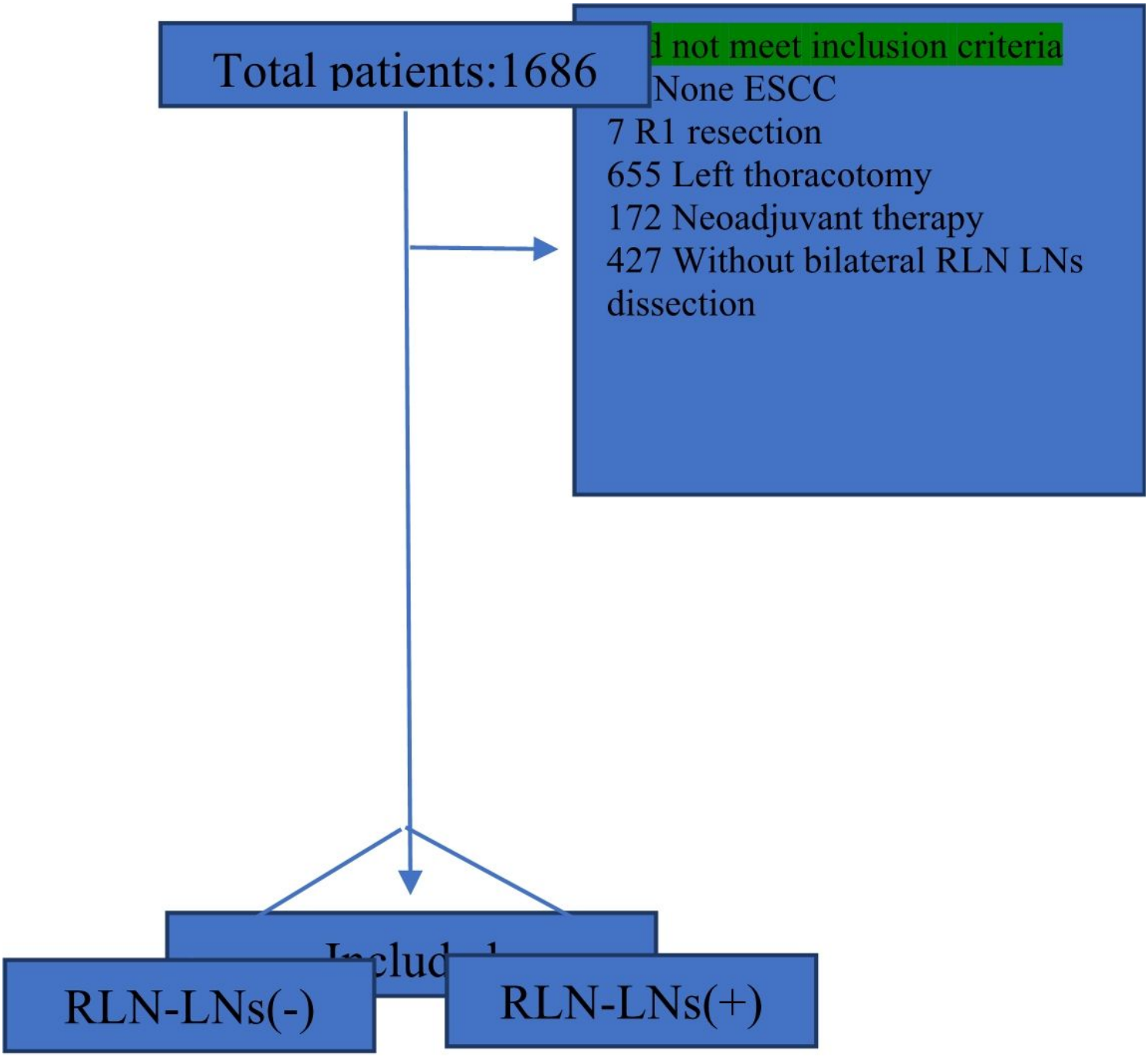

Figure 1

Inclusion flowchart

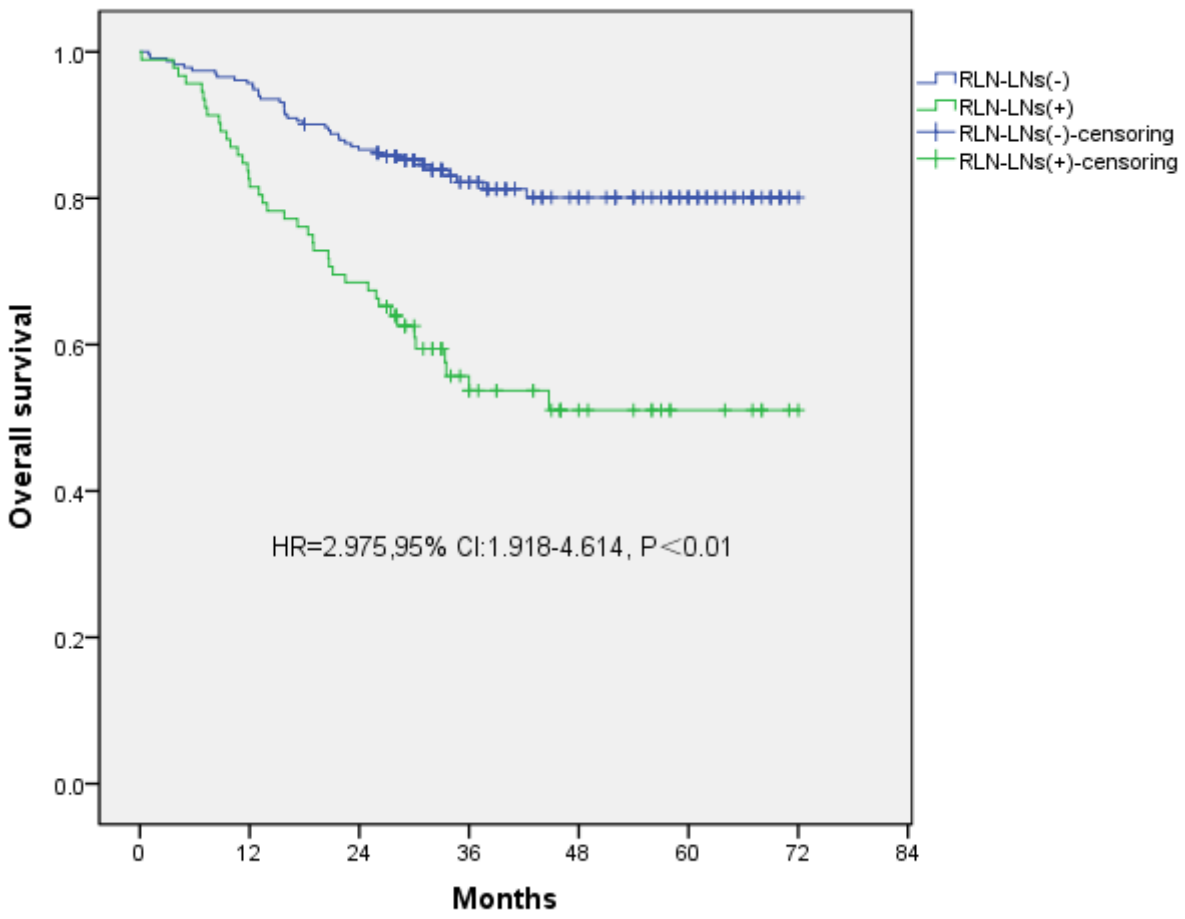

Figure 2

Comparison of overall survival between the patients with positive RLN-LNs and those with negative RLN-LNs. CI, confidence interval; OS, overall survival; HR, hazard ratio

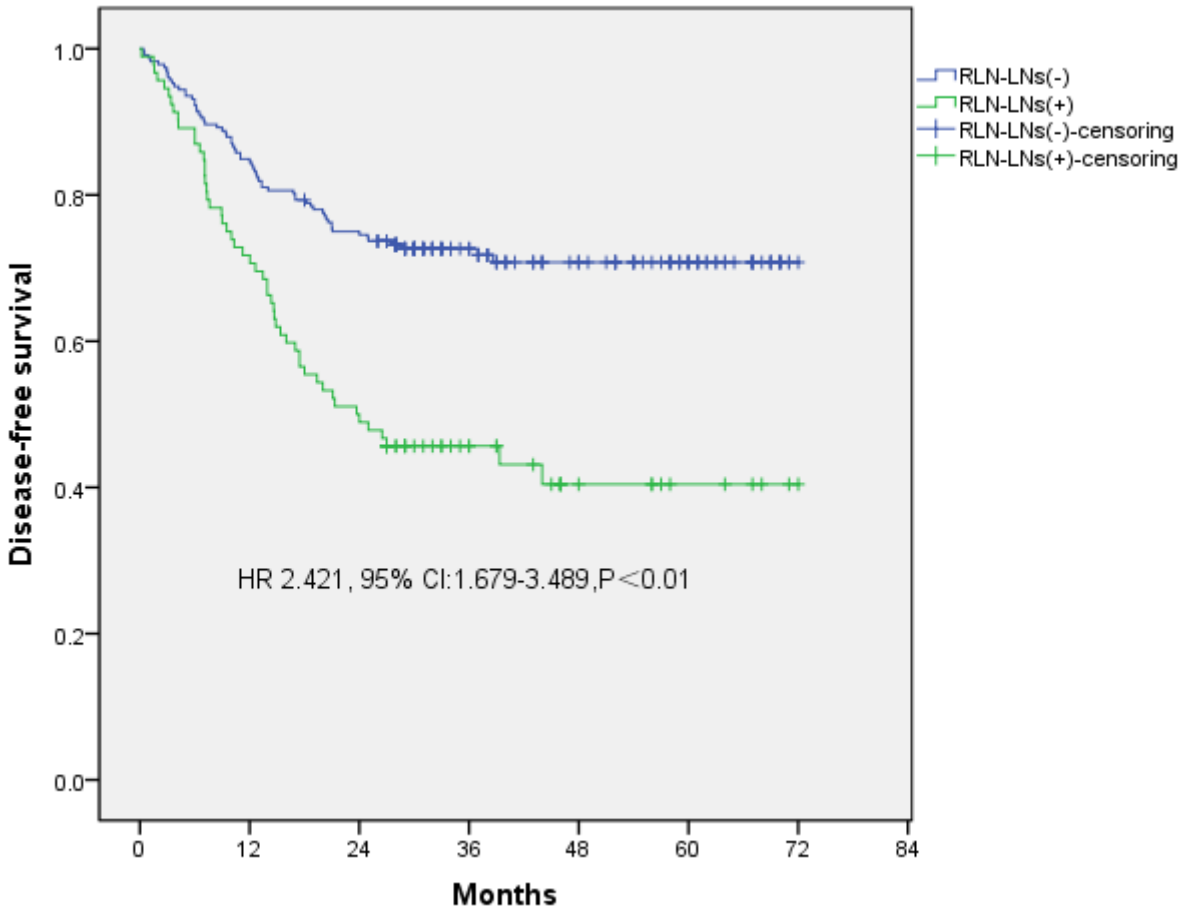

Figure 3

Comparison of disease-free survival between the patients with positive RLN-LNs and those with negative RLN-LNs. CI, confidence interval; DFS, disease-free survival; HR, hazard ratio

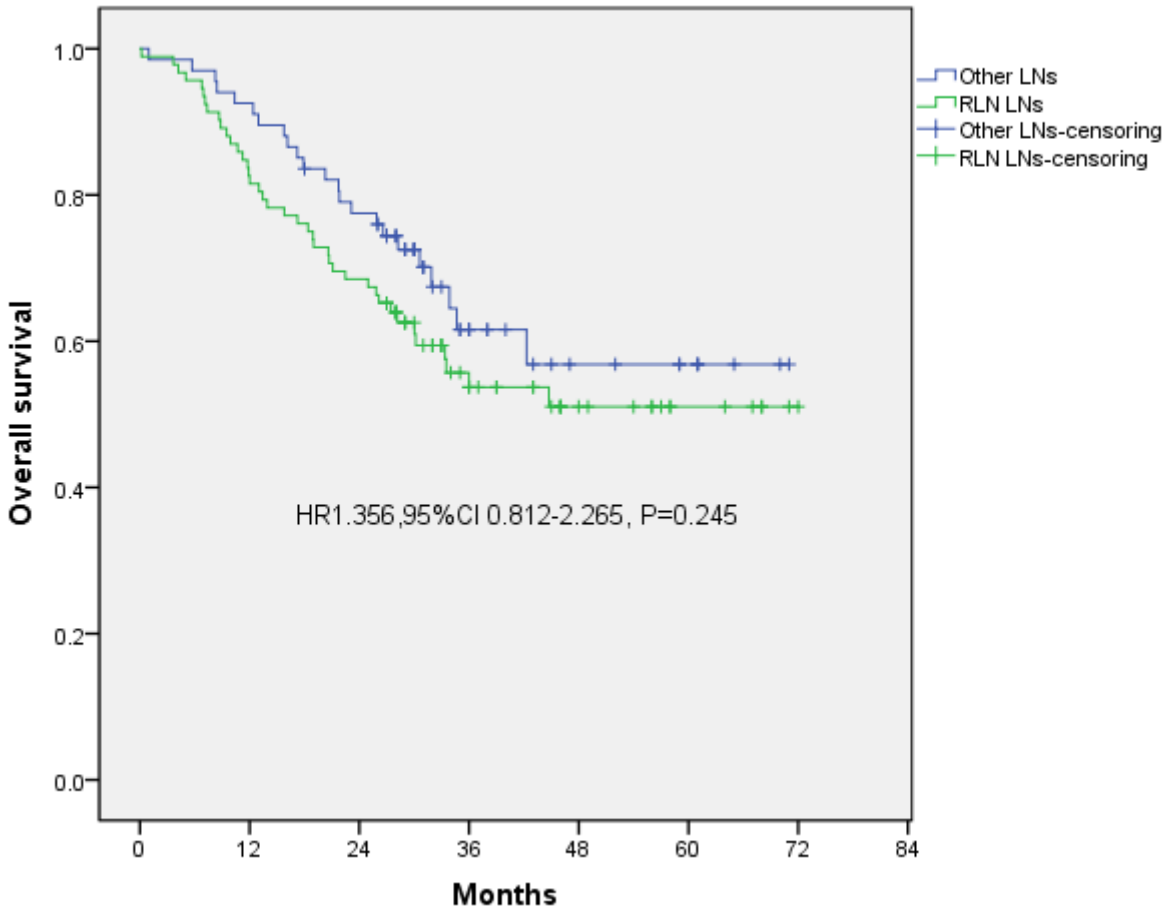

Figure 4

Comparison of overall survival between the patients with positive RLN-LNs and those with positive LNs in the other stations. CI, confidence interval; OS, Overall survival; HR, hazard ratio

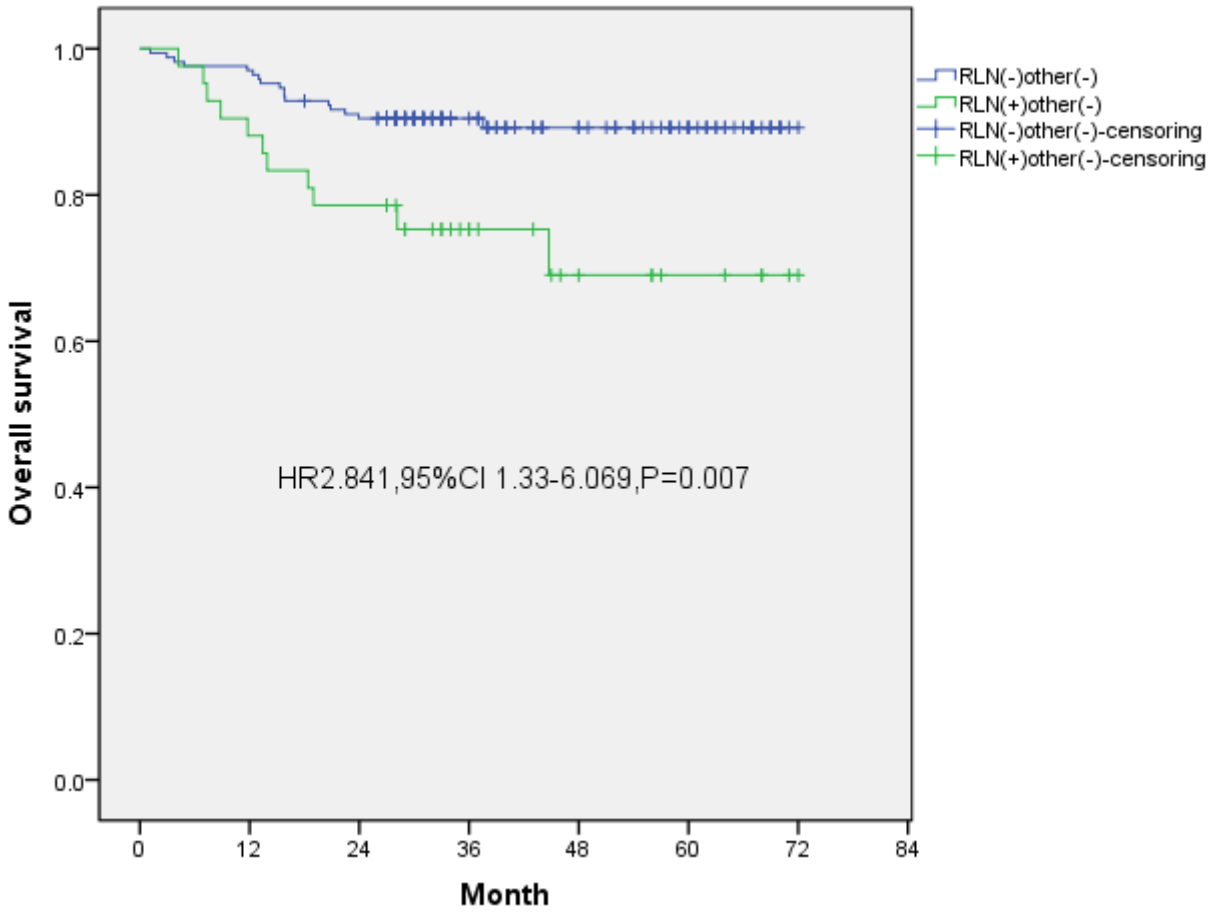

Figure 5

Comparison of overall survival between the patients with only positive RLN-LNs and those without any LNs metastasis. CI, confidence interval; OS, Overall survival; HR, hazard ratio

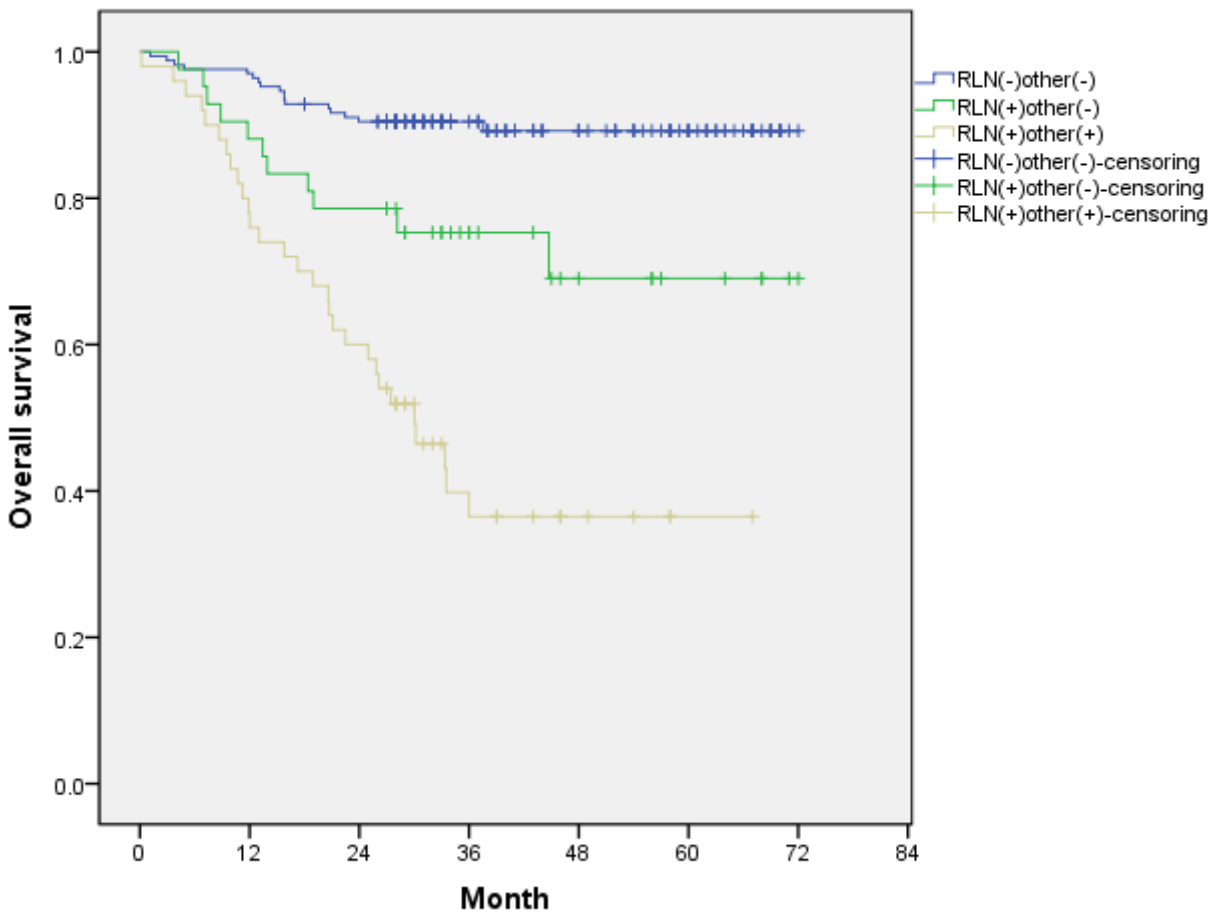

Figure 6

Comparison of overall survival between the patients with RLN-LNs and concurrent other LNs metastasis and with only positive RLN-LNs and those without any LNs metastasis. CI, confidence interval; OS, Overall survival; HR, hazard ratio