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ORIGINAL ARTICLE

Characteristics and clinical significance of recurrent laryngeal nerve lymph node metastasis in esophageal squamous cell carcinoma

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Summary

Purpose: *The recurrent laryngeal nerve lymph nodes (RLN LNs) are among the most common metastatic sites in esophageal cancer, and the dissection of these lymph nodes (LNs) is considered beneficial. The purpose of this study was to evaluate the characteristics of RLN LN metastases from esophageal squamous cell carcinoma, and the effects of these metastases on the prognosis of patients. In addition, we aimed to determine the reasonable range of dissection of regional LNs.*

Methods: *The clinical data from 348 patients who underwent resection for esophageal carcinoma were retrospectively analyzed.*

Results: *Recurrent laryngeal nerve palsy occurred in 37.6% of the patients. In a subgroup of patients with lower esophageal tumors, cervical LN metastases were significantly more common in patients with positive rather than negative RLN LNs. The primary tumor site, tumor differentiation, and tumor invasion depth were factors that significantly influenced RLN LN metastasis. Multivariate analysis revealed that RLN LN metastasis was a significant factor associated with overall survival (OS) and disease-free survival (DFS) ($p<0.001$).*

Conclusion: *Metastasis to RLN LNs is a reliable indicator of cervical LN metastasis in middle/lower thoracic esophageal cancer. RLN LN metastasis may act as a prognostic indicator for patients with esophageal squamous cell carcinoma.*

Key words: *esophageal cancer, lymph node, metastasis, recurrent laryngeal nerve, survival*

Introduction

Esophageal cancer is one of the most common malignant tumors in the world, and remains one of the most deadly. The majority of cases of esophageal cancer are squamous cell carcinoma [1-3].

As a common malignant solid tumor, the main methods of treatment for esophageal cancer include surgery, radiotherapy, chemotherapy, traditional Chinese Medicine, and immunotherapy [4]. Among them, surgery is the primary method of treatment. In recent years, surgical methods have advanced. However, at home and abroad, the 5-year overall survival rate after conventional resection of esophageal carcinoma is only 20–30% [5].

LN metastasis is a key factor in surgical staging and prognosis [6]. Skip LN metastasis can occur. RLN LNs are among the most common metastatic sites in esophageal cancer. Previous studies suggested that the RLN LNs may be considered as sentinel LNs [7,8]. However, the prognostic value of RLN LNs in esophageal cancer remains controversial [9-11].

Therefore, we retrospectively analyzed the clinical and pathological data of 348 cases of esophageal squamous cell carcinoma accompanied with RLN LN metastasis. We aimed to evaluate the characteristics of LN metastases near the RLN

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from esophageal squamous cell carcinoma and the effect of these metastases on the patient prognosis. Furthermore, we aimed to determine the reasonable range of dissection of regional LNs.

Methods

Patients

From January 2000 to December 2009, 348 patients with esophageal cancer were treated at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, including 281 males and 67 females, aged from 36–78 years (average: 57.8±7.7 years; median: 58.0 years). All patients were diagnosed preoperatively with thoracic esophageal carcinoma by electronic gastroscopy. In addition, patients underwent neck, chest, and abdominal computed tomography (CT) to clarify the preoperative TNM stage. Neoadjuvant therapy was not performed preoperatively. Preoperative examination showed no evidence of surgical contraindications, and informed consent was provided by the patients.

Surgical methods

Patients underwent right thoracic incision subtotal esophagectomy, with bilateral cervical, thoracic, and abdominal three-field lymphadenectomy. We cut off the fifth rib through right lateral incision, entered the thoracic cavity, and disconnected the esophagus. Intrathoracic, middle, and lower mediastinal LNs were removed. The chest was closed and patients were changed to the supine position. Cervical collar midline incisions were performed at the same time, along with neck LN dissection. A gastric tube was inserted for reconstruction of the alimentary tract after resection of esophageal tumors.

Resection of right RLN LNs: Behind the trachea, mediastinal pleura was exposed up to the right subclavian artery. Along the vagus nerve trunk, about 1 mm away from the vessel upstream of the tracheoesophageal groove, the RLN was exposed to the level of the right subclavian artery and the surrounding LNs and fatty tissues were removed.

Resection of left RLN LNs: the left RLN bypassed the aortic arch ascending to the left. The esophagus was freed to the parietal pleura, and was pulled back.

Concurrently, the assistant surgeon pulled the trachea to the front, slightly behind, and to the left of the trachea, and blunt dissection was carefully performed. It was easy to free the left RLN. The 1-mm diameter nerve was separated to the root of the neck, and the surrounding LNs and fatty tissues were cleared.

Follow-up

For the first year, follow-up of outpatients was carried out every 3 months, including routine physical examination and chest and abdominal CT. Electronic gastroscopy was performed at the end of 1 year. Afterward, one follow-up was performed every 6 months and gastroscopy was performed at the end of each year. The determination of long-term survival began from the first days after surgery and ended in December 2012.

Survival rates were determined with the Kaplan-Meier method and compared by log-rank test. OS and DFS were both analyzed. OS was counted from the day of surgery until death, and DFS was defined as the time from surgery until tumor recurrence.

Statistics

SPSS16.0 software was used for data analysis. The correlation of clinical and pathological parameters was assessed by Pearson's x^2 test. Survival analysis was performed using the Kaplan-Meier method, and differences in survival curves were compared by log-rank test. Univariate and multivariate analyses were carried out by Cox regression and logistic regression and $p<0.05$ was considered statistically significant.

Results

Lymph node metastasis

Among 348 cases of esophageal cancer, 131 (37.6%) cases had RLN LN metastasis. There were 1218 right and left RLN LNs detected, with an average of 9.3 lymph node dissections per patient; 299 (24.5%) cases had LN metastasis. In this study, the rate of metastasis of right RLN LNs was 20.7% (72/348), slightly higher than that of left RLN LNs 17.0% (59/348). The incidence of skip metastasis of RLN LNs was 4.9% (17/348).

Correlation between RLN LNs and cervical lymph nodes

We analyzed and compared the relationship between RLN LNs and cervical LNs. Among the 131 patients with RLN LN metastasis, 73 (55.7%) had cervical LN metastasis; among the 217 patients without RLN LN metastasis, only 64 (29.5%) had cervical LN metastasis. Further analysis showed that cervical LNs correlated with the middle and lower esophagus were responsible for RLN LN metastasis. In patients with RLN LN metastasis, the cervical LN metastasis rate was 60.0% (42/70) in middle esophageal carcinoma patients, and 24.1% (39/162) in patients without RLN LN metastasis. The difference was statistically significant ($p=0.018$). In the lower esophageal cancer patients, the cervical LN metastasis rates were 48.7% (19/39) and 27.8% (5/18) in patients with and without RLN LN metastasis, respectively ($p<0.05$).

RLN LN metastasis in middle and lower esophageal cancer patients had a predictive effect on cervical LN metastasis. However, RLN LN metastasis in patients with upper esophageal cancer had no predictive effect on the rate of LN metastasis (Table 1).

Correlation analysis of clinicopathological parameters and RLN LN metastasis

Correlation analysis of RLN LN metastasis and clinicopathological parameters in patients with esophageal carcinoma showed that RLN LN metastasis was correlated with T staging, tumor location, tumor differentiation, and number of metastatic LNs. Compared with T1–T2 tumor tissues, the rates of RLN LN metastasis with T3–T4 tissues were higher (p=0.004).

In tissues with more LN metastases, the rate of RLN LN metastasis increased significantly (p<0.001); RLN LN metastasis occurred easily in the lower esophageal cancer patients and in patients with poorly differentiated esophageal tumors (p=0.001 and p=0.003, respectively). Moreover, RLN LN metastasis showed no correlation with sex or tumor size (Table 2).

Correlation between RLN LNs, OS, and DFS

The relationships between RLN LNs, OS and DFS of patients with esophageal cancer were analyzed by log-rank test. The results showed that OS and DFS were shorter in patients with RLN LN metastasis than those with no RLN LN metastasis (Figure 1).

T stage, tumor differentiation, and LN metastasis were also used to analyze the relationship between RLN LN metastasis and OS. The results also showed that OS and DFS were shorter in patients with RLN LN metastasis (p<0.001; Figures 2-4).

Univariate and multivariate analysis of prognostic factors influencing the survival of patients with esophageal cancer

Cox univariate regression analysis showed that clinical stage, tumor size, tumor location, and RLN LN metastasis were risk factors for the prognosis of patients with esophageal cancer (Table 3).

The dependent variable was used for the prognosis of patients with the above risk factors. The differences that were statistically significant in univariate analysis were used as independent variables. The Cox regression model was used for multivariate analysis. The results showed that

Table 1. The relationship between RLN LN metastasis and cervical LN metastasis

Tumor site	*Frequency of cervical LN metastasis (n=137)*		*p value*
	RLN LN(+) (%)	*RLN LN(–) (%)*	
Upper esophagus	12/22(54.5)	20/37(54.0)	0.814
Middle esophagus	42/70(60.0)	39/162(24.1)	0.001
Lower esophagus	19/39(48.7)	5/18(27.8)	0.022

Table 2. Relationship between RLN LN metastasis and clinicopathological characteristics of esophageal cancer

Characteristics	*RLN LNs metastasis*		*p value*
	Negative n (%)	*Positive n (%)*	
Age at diagnosis/years			0.005
≤55	79 (73.1)	29 (26.9)	
>55	138 (57.5)	102 (42.5)	
Sex			0.105
Male	181 (64.4)	100 (35.6)	
Female	36 (53.7)	31 (46.3)	
Tumor location			0.001
Upper esophagus	37 (62.7)	22 (37.3)	
Middle esophagus	162 (69.8)	70 (30.2)	
Lower esophagus	18 (31.6)	39 (68.4)	
Tumor size (cm)			0.779
≤5.0	178 (62.0)	109 (38.0)	
>5.0	39 (63.9)	22 (36.1)	
T stage			0.004
T1	37 (86.0)	6 (14.0)	
T2	71 (58.2)	51 (41.8)	
T3	100 (61.0)	64 (39.0)	
T4	9 (47.4)	10 (52.6)	
Differentiation			0.003
G1	18 (40.0)	27 (60.0)	
G2	150 (64.4)	83 (35.6)	
G3	49 (70.0)	21 (30.0)	
No. of metastatic nodes			<0.001
1-2	105 (70.0)	45 (30.0)	
3-6	73 (65.8)	39 (34.2)	
≥7	39 (44.8)	48 (55.2)	

Table 3. Univariate analysis of prognostic factors influencing the survival of patients with esophageal cancer

Progn. factors	*HR*	*95% CI*	*p value*
Age (continuous variable)	1.294	0.721–2.323	0.127
Sex	1.067	0.856–1.330	0.561
T stage	0.483	0.328–0.710	<0.001
Tumor size	1.438	1.042–1.984	0.027
Tumor location	1.325	1.109–1.584	0.002
Differentiation	1.238	0.980–1.562	0.073
RLN LN metastasis	3.463	2.527–4.746	<0.001
Cervical lymph node metastasis	0.886	0.723–1.052	0.742

HR: hazard ratio, CI: confidence interval, RLN LN: recurrent laryngeal nerve lymph node

Table 4. Multivariate analysis of prognostic factors influencing the survival of patients with esophageal cancer

Progn. factors	*HR*	*95% CI*	*p value*
T stage: T_1+T_2 / T_3+T_4	1.512	1.248–1.807	<0.001
Location of tumor: upper/others	1.238	0.939–1.633	0.130
Tumor size, cm (≤ 5.0/> 5.0)	1.319	0.952–1.828	0.096
RLN LN metastasis (yes/no)	3.361	2.449–4.612	<0.001

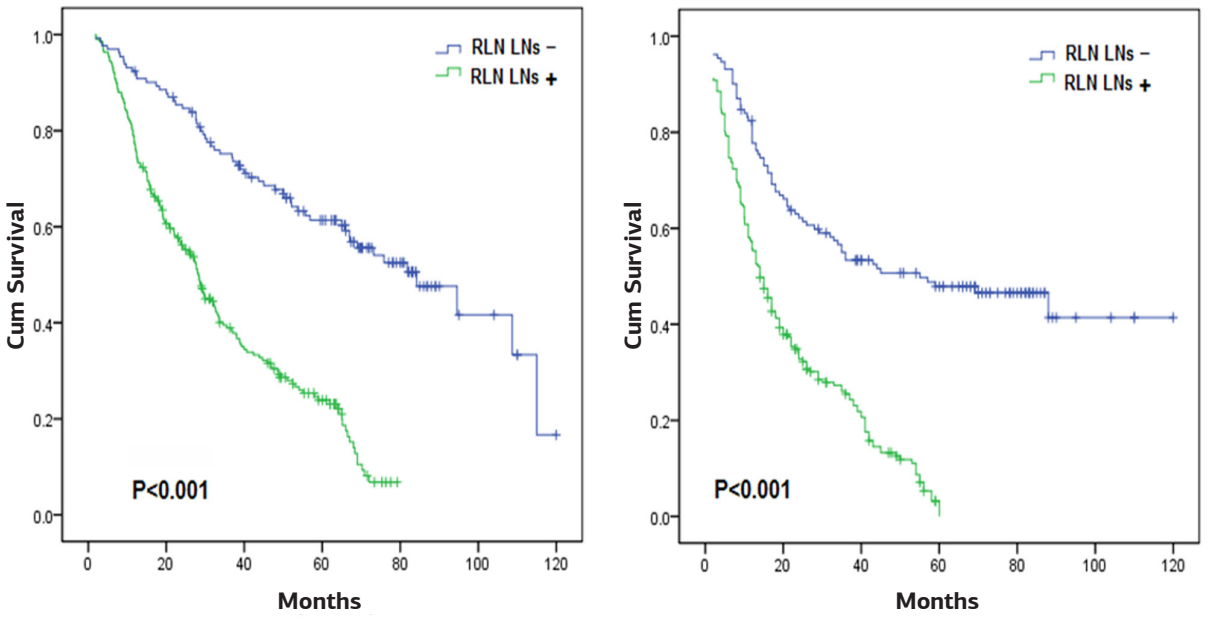

Figure 1. Kaplan-Meier survival analysis for OS and DFS of RLN LN metastasis in esophageal cancer patients.

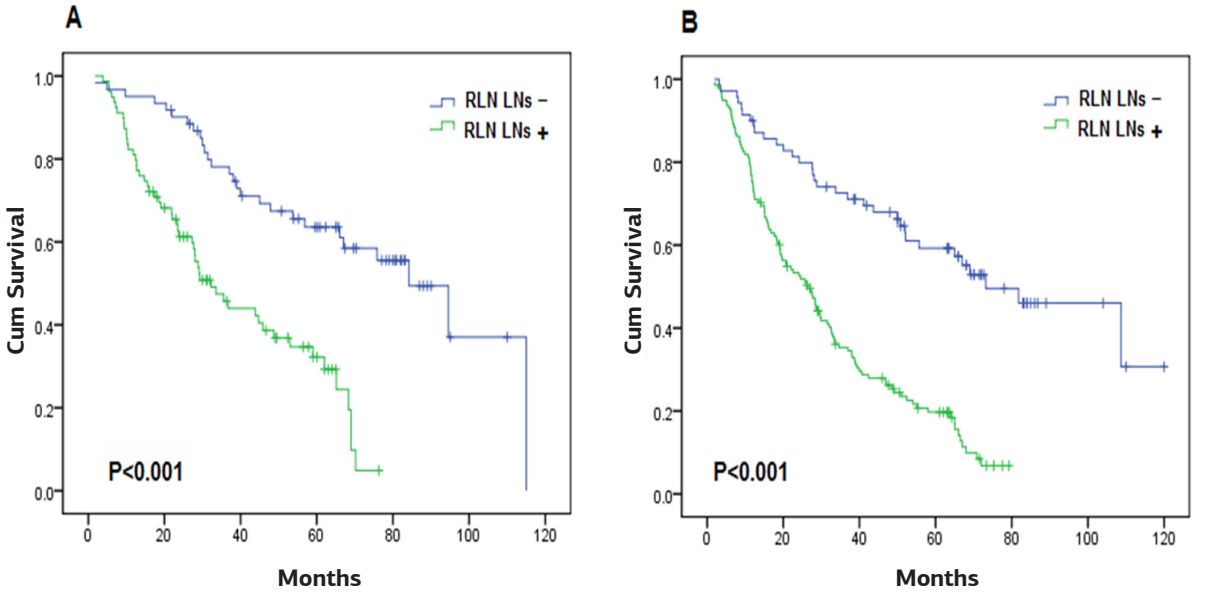

Figure 2. Effects of RLN LN metastasis on the survival of esophageal cancer patients with stage pT1–2 **(A)** and stage pT3-4 **(B)**.

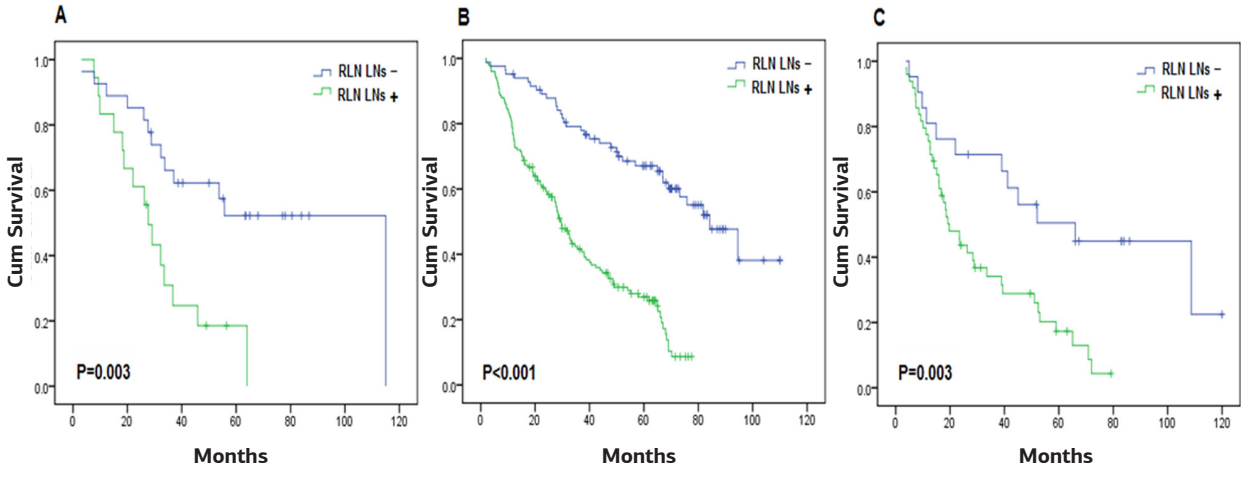

Figure 3. Effects of RLN LN metastasis on the survival of esophageal cancer patients with G1 **(A)**, G2 **(B)**, and G3 **(C)**.

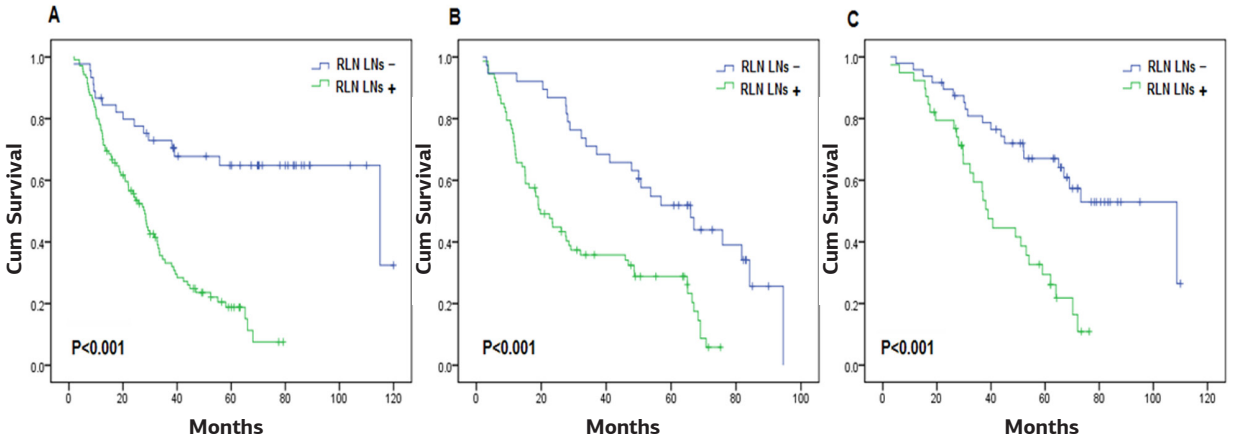

Figure 4. Effects of RLN LN metastasis on the survival of esophageal cancer patients with No. of metastatic nodes from 1–2 **(A)**, No. of metastatic nodes from 3–6 **(B)**, and No. of metastatic nodes ≥ 7 **(C)**.

T staging and metastasis were risk factors of RLN LN metastasis in patients with esophageal carcinoma LN metastasis (Table 4).

Postoperative complications

The incidence of laryngeal nerve injury was 0.86% (3/348), the incidence of anastomotic stoma was 2.01% (7/348), the incidence of chylous and lymph fistula were 0.86% (3/348), and the incidence of pulmonary infection was 3.16% (11/348).

Discussion

Lymphatic metastasis is the main pathway of metastasis of esophageal carcinoma. The esophageal submucosa is rich in lymphatic vessels that form a dense network to communicate with the mediastinum. Therefore, cancer cells can give skip metastases through this network. Lymphatic metastasis is therefore particularly complex. Conventional esophagectomy can result in poor prognosis. Mediastinal and cervical LN metastasis are the main causes of local recurrence after resection of esophageal carcinoma, and the bilateral RLN LNs are the most common sites of metastasis from thoracic esophageal carcinoma. The LN metastasis pathway from the mediastinum and neck is a key part of tumor metastasis [12-14]. Hoarseness occurs in patients with esophageal cancer, mostly caused by compression of the tracheoesophageal groove from metastatic LNs on the RLN. Therefore, analyzing LN metastasis of the RLN in esophageal cancer is helpful for selecting the operation method, determining the scope of LN dissection and guiding the postoperative treatment plan.

Previous studies reported that the rate of metastasis of RLN LNs in esophageal carcinoma is 20–50% [15-19]. This study showed that the rate of RLN LN metastasis was 37.6%, and its occurrence had no relation with tumor location, grade of differentiation, or depth of invasion.

We analyzed the correlation of clinicopathological parameters and RLN LN metastasis and found that T staging, tumor location, differentiation, and the number of LN metastases were key factors determining RLN LN metastasis. The rates of metastasis of upper, middle, and lower esophageal cancer were 37.3, 30.2, and 68.4%, respectively, indicating that RLN LN transfer rates were higher when the lesions were close to the distal end. The RLN LN metastasis rates of well, moderately well and poorly differentiated tumors were 30.0, 35.6 and 60.0%, respectively. The RLN LN metastasis rates of tumors with T1, T2, T3, and T4 postoperative pathological staging were 14.0, 41.8, 39.0 and 52.6%, respectively, indicating that RLN LN metastasis is closely associated with tumor differentiation and depth of infiltration.

Previous studies showed that the cervical LN metastasis rate of esophageal cancer was 16-43%, and the recurrence rate was 6-16% [20-22]. Therefore, the prediction and detection of cervical LN metastasis in esophageal cancer is important for improving surgical efficacy. In our study, the rate of cervical LN metastasis in esophageal cancer patients with RLN LN metastasis was 55.7%, which was significantly higher than that in patients with no RLN LN metastasis (29.5%). We believe that RLN LNs are key sites of cervical LN metastasis in esophageal cancer, and can be used as sentinel LNs for detecting esophageal cancer metastasis. According to the different esophageal tumor locations, the results from middle and lower esophageal cancer patients indicated that if there is metastasis, the role of cervical LN metastasis is more important than in upper esophageal cancer. This may be because the upper esophagus is relatively closer to the neck, and tumor cells do not appear

to directly metastasize to cervical LNs. This observation was similar to the results of Shiozaki et al. and Veda et al. [23,24].

Tabira et al. [25] showed that RLN LNs are not only a reliable predictor of cervical LN metastasis, but also an independent prognostic factor. Prognostic analysis of RLN LNs and metastasis in esophageal cancer patients in our study showed that RLN LN metastasis can affect the overall survival of patients with esophageal cancer. Further analysis of T staging, tumor differentiation, and number of metastatic LNs stratified the relation between RLN LNs and metastasis of esophageal carcinoma. RLN LN metastasis was found to affect overall survival of patients with esophageal carcinoma, suggesting that RLN LNs should be resected in both the T1/T2 and T3/T4 stages of esophageal carcinoma independent of grade of differentiation.

The dissection of RLN LNs in esophageal cancer can easily cause recurrent laryngeal nerve injury. In this study, the incidence of hoarseness was 0.86% (3/348). RLN LN dissection is a key factor in two-field and three-field LN dissection. To protect the recurrent laryngeal nerve, thoughtful surgical methods were performed [21-24].

In this study, pulmonary infection occurred in 11 cases (3.16%). No operative deaths occurred in this study.

In conclusion, roughly one-third of patients with esophageal carcinoma have RLN LN metastasis. It occurs easily in the lower thoracic segment, and with esophageal cancer that is poorly differentiated and with high invasion depth. RLN LN metastasis is closely correlated with cervical LN metastasis. RLN LN metastasis is an independent prognostic factor in patients with esophageal cancer.

Conflict of interests

The authors declare no conflict of interests.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29.
3. Chen W, Zheng R, Zeng H, Zhang S. The updated incidences and mortalities of major cancers in China, 2011. Chin J Cancer 2015;34:502-507.
4. Ohashi S, Miyamoto S, Kikuchi O, Goto T, Amanuma Y, Muto M. Recent Advances From Basic and Clinical Studies of Esophageal Squamous Cell Carcinoma. Gastroenterology 2015;149:1700-15.
5. Straatman J, Joosten PJ, Terwee CB, Cuesta MA, Jansma EP, van der Peet DL. Systematic review of patient-reported outcome measures in the surgical treatment of patients with esophageal cancer. Dis Esophagus 2015;7:760-72.
6. Cho JW, Choi SC, Jang JY et al. Lymph Node Metastases in Esophageal Carcinoma: An Endoscopist's View. Clin Endosc 2014;47:523-9.
7. Shiozaki H, Yano M, Tsujinaka T et al. Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. Dis Esophagus 2001;14:191-196.
8. Mizutani M, Murakami G, Nawata S, Hitrai I, Kimura W. Anatomy of right recurrent nerve node: why does early metastasis of esophageal cancer occur in it? Surg Radiol Anat 2006;28:333-8.
9. Altorki NK, Zhou XK, Stiles B et al. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg 2008;248:221-226.
10. van der Schaaf M, Johar A, Wijnhoven B, Lagergren P, Lagergren J. Extent of lymph node removal during esophageal cancer surgery and survival. J Natl Cancer Inst 2015;107(5).
11. Hu Y, Hu C, Zhang H, Ping Y, Chen LQ. How does the number of resected lymph nodes influence TNM staging and prognosis for esophageal carcinoma? Ann Surg Oncol 2010;17:784-90.
12. Jiao W, Wang J, Liu Q et al. Lymph node metastasis patterns and influencing factors in patients with limited esophageal small cell carcinoma. Zhonghua Zhong Liu Za Zhi 2015;37:899-903.
13. Jang HJ, Lee HS, Kim MS, Lee JM, Zo JI. Patterns of lymph node metastasis and survival for upper esophageal squamous cell carcinoma. Ann Thorac Surg 2011;92:1091-97.
14. Shiozaki H, Yano M, Tsujinaka T et al. Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. Dis Esophagus 2001;14:191-96.
15. Sato F, Shimada Y, Li Z et al. Paratracheal lymph node metastasis is associated with cervical lymph node metastasis in patients with thoracic esophageal squamous cell carcinoma. Ann Surg Oncol 2002;9:65-70.
16. Ye K, Xu JH, Sun YF, Lin JA, Zheng ZG. Characteristics and clinical significance of lymph node metastases near the recurrent laryngeal nerve from thoracic esophageal carcinoma. Genet Mol Res 2014;13:6411-19.
17. Wu J, Chen QX, Zhou XM, Mao WM, Krasna MJ. Does recurrent laryngeal nerve lymph node metastasis re-

ally affect the prognosis in node-positive patients with squamous cell carcinoma of the middle thoracic esophagus? BMC Surg 2014;14:43.

18. Li H, Yang S, Zhang Y, Xiang J, Chen H. Thoracic recurrent laryngeal lymph node metastases predict cervical node metastases and benefit from three-field dissection in selected patients with thoracic esophageal squamous cell carcinoma. J Surg Oncol 2012;105:548-552.
19. Taniyama Y, Miyata G, Kamei T et al. Complications following recurrent laryngeal nerve lymph node dissection in oesophageal cancer surgery. Interact Cardiovasc Thorac Surg 2015;20:41-6.
20. Murakami H, Nishikawa K, Hirao M et al. A Case of Combined Modality Therapy for a Cervical Lymph Node Recurrence after Surgery for Esophageal Cancer. Gan To Kagaku Ryoho 2015;42:1626-28.
21. Nakashima S, Shiozaki A, Fujiwara H et al. Analysis of thoracic esophageal squamous cell carcinoma with single lymph node metastasis. Gan To Kagaku Ryoho 2014;41:2000-02.
22. Kosugi S, Kawaguchi Y, Kanda T et al. Cervical lymph node dissection for clinically submucosal carcinoma of the thoracic esophagus. Ann Surg Oncol 2013;20:4016-21.
23. Shiozaki H, Yano M, Tsujinaka T et al. Lymph node metastasis along the recurrent nerve chain is an indication for cervical lymph node dissection in thoracic esophageal cancer. Dis Esophagus 2001;14:191-6.
24. Ueda Y, Shiozaki A, Itoi H et al. Intraoperative pathological investigation of recurrent nerve nodal metastasis can guide the decision whether to perform cervical lymph node dissection in thoracic esophageal cancer. Oncol Rep 2006;16:1061-66.
25. Tabira Y, Yasunaga M, Tanaka M et al. Recurrent nerve nodal involvement is associated with cervical nodal metastasis in thoracic esophageal carcinoma. J Am Coll Surg 2000;191:232-7.