

Complications After Lymph Node Dissection Along Bilateral Recurrent Laryngeal Nerves Through Right Thoracic Approach in the Patients With Thoracic Esophageal Cancer

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Abstract

Background: Extensive lymph nodes dissection can improve the accuracy of tumor staging and prognosis of the patients with thoracic esophageal cancer, palsy of recurrent laryngeal nerve (RLN) caused by the lymph node (LN) dissection along RLN chain also increase postoperative complications and may affect the prognosis. This study aimed to evaluate the associated postoperative complications after LN dissection along RLNs in the patients with thoracic esophageal squamous cell cancer (ESCC).

Methods: 339 eligible patients with thoracic ESCC who underwent radical McKeown or Ivor-Lewis esophagectomy by open or VATS procedures through right thoracic approach with LN dissection along bilateral RLNs were included in this study. Univariate and multivariate logistic regression analysis were conducted to assess the correlation of RLN paralysis (RLNP) with other post-operative complications.

Results: 39 of the 339 patients were diagnosed with RLNP (11.5%) postoperatively. The incidence of RLNP in three-field (3FL) LN dissection was significantly higher than that in the two-field (2FL) LN dissection (24.0% vs 8.0%, $P=0.001$). Compared with the patients without RLNP, the patients with it had a significantly higher incidence of postoperative anastomotic leakage ($P=0.029$), pulmonary complications ($P=0.001$) and much longer hospital stay ($P=0.001$). Two patients died of respiratory failure within 30 days caused by RLNP and were treated by reintubation.

Conclusion: RLNP after LN dissection along bilateral RLN in thoracic ESCC was associated with much higher morbidity such as pulmonary complications, anastomotic leakage, and much longer hospital stay. New technologies are required to reduce RLNP incidence and its associated complications.

Introduction

For locally advanced esophageal carcinoma, esophagectomy with radical lymphadenectomy is still the mainstay of the treatment [1]. Complete 3FL-LN dissection, especially the LN dissection along bilateral RLNs, can not only increase the accuracy of pathological staging, but also improve the prognosis for the patients with thoracic ESCC [2]. However, it can also increase the risk of RLNP and associated with high incidence of complications, such as aspiration, respiratory complication, anastomotic leakage, et al. Permanent RLNP also compromises patients' life quality. Therefore, how to balance the profit and disadvantage from LN dissection along RLNs, which has been debated and is still unclear until present. During extensive LN dissection along RLNs, thermal injury, stretching, compression, or vascular damage of the RLN may cause RLNP [3]. The incidence of RLNP after esophagectomy was reported ranging from 10.0%-58.9% [4-9]. Which clinicopathological factors affect the incidence of RLNP during esophagectomy and whether RLNP compromise the patients' survival and life quality has not been clarified. Therefore, this retrospective study aimed to investigate the risk factors of RLNP and its associated post-operative complications as well as prognostic role in the patients with ESCC.

Methods

Inclusion criteria

From March 2015 to December 2018, totally, 1686 patients with 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 LNs dissection along bilateral recurrent laryngeal nerves ;(4) negative pathological resection margin ;(5) through right chest;(6) without preoperative suspected distant metastasis. Finally, 339 patients in total were selected into this study.

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.

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/left 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, a handsewn or stapled gastro-esophageal anastomosis was carried out.

Preoperative assessment and Diagnosis of RLNP

Chest computed tomography, bone scanning, brain MRI, and abdominal ultrasonography were performed in all patients preoperatively to exclude distant metastasis. All specimens were pathologically diagnosed at the Department of Pathology in our institution. The seventh edition UICC esophageal cancer staging criteria was used for TNM classification, and pathology results determined the T and N stage. RLNP was diagnosed based on clinical symptoms such as hoarseness/aspiration/difficult in coughing.

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 with 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

Clinical and Pathologic characteristics of 339 patients

The clinical and pathologic characteristics of the study population are summarized in Table 1. Ages ranged from 40-80 years (average 60.6 years). There were 282 men and 57 women. 74 tumors were in the upper third segment of the thoracic esophagus, 188 in the middle third, 77 in the lower third. All 339 patients underwent subtotal esophagectomy through a right thoracotomy. 75 underwent 3-FL lymph node dissection, and the other 264 underwent 2-FL lymph node dissection. According to the seventh edition UICC esophageal cancer staging criteria, there were 101 cases in T1, 61 cases in T2, 160 cases in T3, 17 cases in T4; 43 cases of well differentiated, 181 cases of moderately differentiated, 115 cases of poorly differentiated.

Table 1
Clinical and Pathologic characteristics of 339 patients

Characteristics	Number of Patients(percentage)
Total cases	339
Age,years	40-80(average 60.6)
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%)
TNMstage	

Characteristics	Number of Patients(percentage)
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%)

LN metastasis

Among the 339 patients with thoracic ESCC, 96 experienced recurrent laryngeal nerve LN metastasis (28.3%). A total of 2279 recurrent laryngeal nerve LNs were detected, and a mean of 6.7 LNs were dissected; 186 metastatic LNs were detected, and the rate of LN metastasis was 8.2%. The rate of patients with right recurrent laryngeal nerve LN metastasis was 22.4%, which was significantly higher than the rate of patients with left recurrent laryngeal nerve LN metastasis (13.9%, $P=0.004$).

Post-operative complications

Postoperative complications occurred in 138 patients (40.7%). Of the 138 patients, 9 patients (2.7%) had chylothorax, of which 2 patients underwent thoracic duct ligation due to the failure of conservative treatment, and 1 patient got fully recovered after being transferred to ICU due to severe chylothorax. 7 patients (2.1%) had postoperative hemorrhage. 2 patients with chest hemorrhage underwent thoracotomy hemostasis, 1 patient with abdominal hemorrhage underwent laparotomy hemostasis. And 1 patient with thoracic hemorrhage and the other 3 patients with incision hemorrhage were cured conservatively. 28 patients (8.3%) had anastomotic leakage, and 3 of them developed tracheoesophageal leakage, all of them got fully recovered after conservative treatment. 75 patients (22.1%) had postoperative pulmonary complications. Of these patients, 8 patients were transferred to intensive care unit (ICU) due to respiratory failure, 7 of the 8 patients were reintubated, 1 patient had tracheotomy eventually, and 2 of them died within 30 days postoperatively. 39 patients (11.5%) had RLNP. 30 patients (8.8%) suffered incision infection. 33 patients (9.7%) had arrhythmia.

Correlation of RLNP and clinicopathologic factors

In the univariate analysis, the incidence of RLNP was significantly correlated with the extent of lymph node dissection (3FL 24.0% versus 2FL 8.0%, $P < 0.001$). Based on the number of metastatic LNs along RLNs, the 339 patients were divided into three groups. the incidence of RLNP increased as the number of metastatic LNs along RLN increased, while no significant difference among each group was observed

(Table 2). Of the 22 patients who underwent open thoracotomy, only 1 patient (4.5%) have RLNP, it was much lower than that in patients underwent MIE (38/317, 12.0%), but there is no statistical difference ($P=0.49$). The RLNP rate was a little higher in patients with upper thoracic esophageal cancer than in patients with middle or lower thoracic esophageal cancer (13.5% vs 10.6% and 11.7%), but there is no significant difference ($P=0.81$). As to other clinicopathologic factors, the results revealed a lack of significant correlation between the recurrent laryngeal nerve LN metastasis and age, gender, tumor length, tumor differentiation and tumor invasion depth ($P>0.05$).

Table 2

Correlation of RLNP with clinicopathologic factors

Characteristics	Category	RLNP(+) (n=39)	RLNP(-) (n=300)	RLNP(+) percentage	P
Gender					
	Male	36	246	12.8%	0.12
	Female	3	54	5.30%	
Age(years)					
	≤60	21	135	13.5%	0.31
	>60	18	165	9.80%	
Tumor length					
	≤5cm	19	101	15.8%	0.076
	>5cm	20	199	9.1%	
Tumor invasion depth					
	T1	13	88	12.9%	0.37
	T2	9	52	14.8%	
	T3	17	143	10.6%	
	T4	0	17	0.0%	
Tumor differentiation					
	Well	5	38	11.6%	0.96
	Moderate	20	161	11.0%	
	Poor	14	101	12.2%	
Primary tumor site					
	Upper	10	64	13.5%	0.81
	Middle	20	168	10.6%	
	Lower	9	68	11.7%	
Lymph node dissection					
	2-FL	18	57	24.0%	<0.001
	3-FL	21	243	8.0%	
Thoracic procedure					

Characteristics	Category	RLNP(+) (n=39)	RLNP(-) (n=300)	RLNP(+) percentage	P
	MIE	38	279	12.0%	0.49
	Open	1	21	4.5%	
Number of metastatic RLN LNs					
	0	25	218	10.3%	0.53
	1-2	11	66	14.3%	
	3-6	3	16	15.8%	
Number of dissected RLN LNs					
	2-5	18	143	11.2%	0.95
	6-10	13	102	11.3%	
	>10	8	55	12.7%	

Correlation of RLNP and other postoperative complications

The correlation of RLNP and other postoperative complications was summarized in the Table 3. Compared with RLNP(-) group, RLNP(+) group had significantly higher anastomotic leakage rate (17.9% vs 7.0%, P=0.029); pulmonary complications (46.2% vs 19.0%, P=0.001); and much longer hospital stay(19.59±11.623 vs 12.63±7.376 days, P=0.001); but similar incision infection rate (10.3% vs 8.7%, P = 0.76) (Table 3).

Table 3
Correlation of RLNP with other postoperative complications

Complications	RLNP(+)(N=39)	RLNP(-)(n=300)	P
Anastomotic leakage	7(17.9%)	21(7.0%)	0.029
Pulmonary complications	18(46.2%)	57(19.0%)	<0.001
Incision infection	4(10.3%)	26(8.7%)	0.76
Reintubation	2(5.1%)	5(1.7%)	0.19
Tracheotomy	1(2.6%)	0	0.12
Tracheoesophageal leakage	1(2.6%)	2(0.7%)	0.31
Transfer to ICU	3(7.7%)	6(2.0%)	0.073
Postoperative hospital stay time(days)	19.59±11.623	12.63±7.376	0.001

Correlation of RLNP with postoperative pulmonary complications

Univariate analysis showed RLNP(OR 3.654, 95%CI 1.828-7.303, P < 0.001), anastomotic leakage(OR 3.481, 95%CI 1.575-7.693, P=0.003), older age (OR 2.483, 95%CI 1.429-4.315, P=0.001) were associated with a higher incidence of pulmonary complications. Multivariate analysis showed that RLNP (OR 2.761, 95%CI 1.873-8.216, P < 0.001),was still an independent risk factors of postoperative pulmonary complications (Table 4).

Table 4
Pulmonary complications: Univariate and Multivariate analysis

Characteristics	Univariate			Multivariate		
	OR	95%CI	P	OR	95%CI	P
Male Gender	1.408	0.674-2.941	0.484			
Age	2.483	1.429-4.315	0.001	2.722	1.52-4.872	0.001
Anastomotic leakage	3.481	1.575-7.693	0.003	2.823	1.22-6.535	0.015
Minimally invasive surgery	0.964	0.343-2.704	1			
Recurrent laryngeal nerve paralysis	3.654	1.828-7.303	<0.001	0.004	1.873-8.216	<0.001
Lymph node yield	0.942	0.505-1.758	1			
Chylothorax	1.792	0.437-7.341	0.42			

Discussion

Esophagectomy with radical lymphadenectomy still plays the most important role in the multimodality treatment for locally advanced esophageal carcinoma. In recent years, complete 2FL- or 3FL-LN dissection along the esophagus, especially along the bilateral RLNs has been emphasized in the surgical treatment for ESCC. It can not only increase the accuracy of pathological staging, but also improve the prognosis for the patients with thoracic ESCC [2]. However, extensive LN dissection also increase the risk of RLNP and the incidence of associated complications, such as aspiration, respiratory complication, anastomotic leakage, et al. Permanent RLNP also compromises patients' life quality. As reported in the literatures, the incidence of RLNP after esophagectomy ranged from 10.0–58.9% [4–9]. These disparities may be attributed to variation in the extent of lymph node dissection, usage of surgical technique, the T-stage of the primary tumor, and number of metastatic lymph nodes, and surgeons' experience [10–11]. Patients with RLNP may present with symptoms from hoarseness, dyspnea during speech, aspiration, difficulty with coughing and expectation of sputum, and may even suffocate in case of bilateral damage. Consequently, dysfunction of RLNs may result in other post-operative complications such as pneumonia, anastomotic leakage, which prolong hospital-stay and severely compromised the post-operative life quality of the patients with esophageal cancer [12–13]. Our study demonstrated that extensive lymph nodes dissection along recurrent laryngeal nerves increased the risk of RLN injury, and subsequently resulted in high incidence of pneumonia and anastomotic leakage, this is consistent with what reported in the literature [12–13]. The patients with temporary or permanent RLNP after esophagectomy usually

have difficulties with swallowing and coughing, suffer from the associated pulmonary complications, they can't recover smoothly and need much longer treatment and hospital stay. Their life quality was deteriorated and medical cost significantly increased. These results stress the importance of preserving the RLN for both short- and long-term outcomes.

The incidence of RLNP after esophagectomy with radical 2FL or 3FL LN dissection was 11.5% in this series, which is similar to the results of previous studies [4–9]. Our diagnosis of RLNP mainly based on the symptoms such as hoarseness, aspiration, difficulty with coughing except a few by bronchoscopy or esophagoscopy. And most RLNPs were temporary, and most of them recovered within 6 months, indicating that injury of the RLNs might be caused by compression or stretching or compromised blood supply of the nerves other than structure damage. In this study, univariate analysis showed that patients with extensive 3FL lymph node dissection had a higher RLNP rate than that those with 2FL (24.0% vs 8.0%, $P=0.001$) and the incidence of RLNP increased as the number of metastatic LNs along RLN increased. This suggested that more extensive LN dissection could lead to higher RLNP rate and neoadjuvant therapy was needed for patients with suspicious RLN LNs metastasis.

Pulmonary complication was reported to be the most common postoperative complication after esophagectomy [14–15]. Our study showed that RLNP was an independent risk factor for postoperative pulmonary complication. In our study, 8 patients were transferred to ICU due to respiratory failure, 7 of the 8 patients were reintubated, 1 patient had tracheotomy eventually. And 2 of them died within 30 days postoperatively, both of them experienced RLNP. Patients with RLNP could not close the glottis completely, which resulted in pulmonary infection leading to weak coughing, ineffective expectoration aspiration and retention of secretion, which finally result in pulmonary infection even respiratory failure [16]. These results stress the importance of preserving the RLN to decrease the incidence of postoperative pulmonary complications.

Anastomotic leakage is also a common and serious complication after esophagectomy. which does not prolong hospital stay and treatment, but also increase medical expense significantly. [17–19]. Our results showed that the incidence of anastomotic leakage was significantly correlated with RLNP (17.9% vs 7.0%, $P=0.029$). This may be due to the inability of coughing in patients with RLNP, which lead to the rising of pressure in the thoracic cavity and was transmitted to the anastomosis site when patient tried to cough and expect the sputum hardly [8]. Another possible reason may be poor nutritional status caused by difficulty in swallowing, which affects tissue healing [12].

Considering harmful consequences of RLNP, it is impressive to prevent RLNP during esophagectomy. It was reported in literatures that noninvasive intraoperative neurological monitoring (IONM) is safe and feasible, which can help avoid intraoperative RLN injury and reduce the incidence of RLNP [20]. IONM has been a routine application during thyroid surgery to avoid RLN injury, and its positive effects have been proven [21]. Therefore, IONM may enable surgeons to identify and preserve the RLN during lymph nodes dissection near bilateral RLN. The usage of energy instruments such as electric knife, electric hook, and ultrasonic knife brings great convenience to the operation, which can significantly reduce surgical

hemostasis and operation time [22]. However, thermal injury during the use of energy instruments is a substantial reason of RLNP. Therefore, direct contact with the RLN should be avoided and a safe distance of more than 3mm should be maintained when using energy instruments [23]. And it has been proven that the use of non-energy devices such as scissors and hemostatic clips can reduce the incidence of RLNP [24–26].

One limitation of this study is that this is a retrospective study and all patients included were from a single center and operated by a group of surgeons with difference in surgical skills and experience. Another limitation is that diagnosis of RLNP were mainly based on clinical symptoms instead of laryngoscopy.

RLNP after esophagectomy is significantly associated with an increased incidence of pulmonary complication, anastomotic leakage and much longer hospital stay. It is impressive that renovation and usage of new technologies are needed to reduce RLNP.

Declarations

Conflict of Interest Statement: There has no conflict of interest.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was independently approved by the Ethics committee of Cancer Hospital Chinese Academy of Medical Sciences. 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.

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