



# A nomogram prediction model for recurrent laryngeal nerve lymph node metastasis in thoracic oesophageal squamous cell carcinoma

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**Background:** The metastasis rate to the recurrent laryngeal nerve lymph node (RLN LN) is high, but resection of it is challenging and increases complications. This study explored the risk factors for the RLN LN metastasis in thoracic oesophageal squamous cell carcinoma and developed a novel scoring system to predict it.

**Methods:** We retrospectively analysed the clinicopathological data of 265 patients between 2015 and 2018. Univariate and multivariate analyses were performed to screen for risk factors and establish a logistic regression model to predict the risk of RLN LN metastasis. A nomogram was constructed accordingly. Further analyses were conducted regarding right and left RLN LN metastasis alone.

**Results:** (I) The metastatic rates of the left and right RLN LN were 15.1% and 20.4%, respectively. (II) Multivariate logistic regression analysis showed that the short axis diameter of the left RLN LN, short axis diameter of the right RLN LN, maximum diameter of the tumor, tumor location, subcarinal lymph node status and paraoesophageal lymph node status were all independent risk factors for RLN LN metastasis. (III) Multivariate logistic regression analysis showed that the short axis diameter of right RLN LN, tumor location and subcarinal lymph node status were independent risk factors for right RLN LN metastasis. (IV) Multivariate logistic regression analysis showed that short axis diameter of left RLN LN was an independent risk factor for left RLN LN metastasis.

**Conclusions:** The metastatic rates of the left and right RLN LNs were high and can be predicted according to these nomograms.

**Keywords:** Oesophageal cancer; recurrent laryngeal nerve (RLN); lymph node dissection; nomogram; scoring system

Submitted Dec 25, 2018. Accepted for publication Jun 06, 2019.

doi: 10.21037/jtd.2019.06.46

View this article at: <http://dx.doi.org/10.21037/jtd.2019.06.46>

## Introduction

Oesophageal carcinoma is the 8th most common cancer worldwide and the 6th leading cause of cancer-related death, and the 5-year survival rate is only 15–25% worldwide (1). In China (2), the estimated number of new

oesophageal cancer cases and deaths per year are 477.9 and 375.0 thousand, respectively.

Oesophagectomy with 3-field lymphadenectomy increases the overall 5-year survival rate to 40–55.6% (3–7). However, this technique also increases the complexity of the

operation and complications (5-9), especially the dissection of lymph nodes (LNs) around the recurrent laryngeal nerve (RLN) (10-12). Furthermore, not all patients can benefit from the dissection of the RLN LNs (11,12). Prediction of RLN LN metastasis will provide a reference for planning the treatment regimen, selecting the surgical approach and planning for intraoperative LN dissection. Therefore, we retrospectively analysed the clinicopathological data of 265 consecutive oesophageal squamous cell carcinoma (ESCC) patients who underwent oesophagectomy at the General Hospital of the Jinan Military Area and the Second Affiliated Hospital of Shandong University to formulate a statistical model to accurately predict RLN LN metastasis in thoracic ESCC patients.

## Methods

### Study cohort

In this retrospective study, a total of 542 consecutive patients who underwent curative oesophagectomy for oesophageal carcinoma at the General Hospital of the Jinan Military Area and the Second Affiliated Hospital of Shandong University between January 2015 and June 2018 were studied. The clinicopathological data of 265 patients who met the following conditions were collected.

The inclusion criteria were as follows: (I) preoperative or postoperative pathology proven to be primary ESCC; (II) no distant metastasis found on thoraco-abdominal enhanced computed tomography (CT), cervical ultrasonography, electronic gastroscopy, endoscopic ultrasound and (or) whole-body positron emission tomography CT (PET-CT); (III) underwent thoracoscopic-assisted tri-incisional oesophagectomy performed with two- or three-field lymphadenectomy and complete dissection of the RLN LNs; and (IV) complete clinicopathological data. The exclusion criteria were as follows: (I) patients who accepted neoadjuvant chemotherapy or radiotherapy (cases treated by neoadjuvant therapy usually come into pathological changes that cannot be well elucidated by this issue); (II) cases that were combined with other malignant tumours; (III) pathological results revealing other cellular components in addition to squamous cell carcinoma; (IV) patients in whom RLN LN dissection was not performed (postoperative pathological evaluation showing that the number of bilateral RLN LNs was zero); or (V) incomplete clinicopathological data.

### Surgical methods

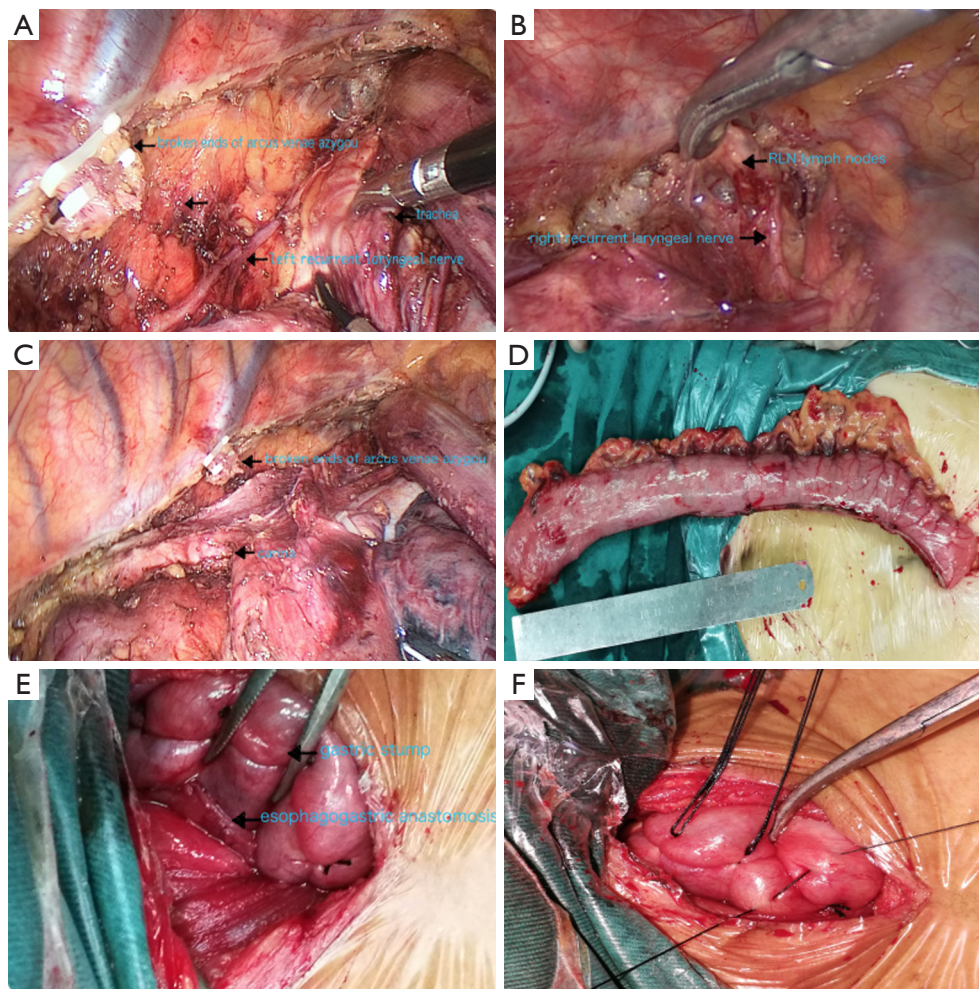
All patients underwent subtotal oesophageal excision by a tri-incisional approach involving thoracoscopic resection of the oesophagus and mediastinal lymphadenectomy in a left semi-prone position, followed by laparoscopic mobilization of the stomach and abdominal LN dissection in a supine position and left-sided cervical anastomosis (Figure 1A,B,C). Extensive lymphadenectomy that involved resection of the bilateral upper mediastinal LNs in addition to standard lymphadenectomy was performed during every operation (Figure 1D,E,F). Cervical lymphadenectomy (32 patients underwent 3-field lymphadenectomy, while 233 patients underwent 2-field lymphadenectomy) was only performed in cases of suspicious cervical LN metastasis by cervical ultrasound or PET-CT. The extent of RLN LN dissection and determination of the tumour location were defined in accordance with the Japanese Classification of Esophageal Cancer, 11th edition: parts II and III (13).

The left RLN LNs were dissected as follows. First, the upper thoracic oesophagus was removed from the oesophageal bed, and the left RLN was dissected from the dorsal side of the aortic arch and moved upward to the left tracheoesophageal groove. LNs and surrounding fatty tissues around the nerve were completely dissected (Figure 1A). The right RLN LNs were dissected as follows: we first exposed the right subclavian artery by removing the mediastinal pleura above the azygos arch. The right RLN originates from the vagus nerve trunk at the level of the right subclavian artery and extends upward to the lower pole of the thyroid. The LNs together with the surrounding fatty tissues were removed carefully (Figure 1B).

Surgically dissected LNs were classified according to the definition of regional LNs, given individual names or numbers and sent to pathologists. The LNs that were dissected *en bloc* with the oesophagus were isolated from the specimen before fixation. All of these primary tumour samples were fixed in 10% neutral buffered formalin, embedded in paraffin and stained with haematoxylin and eosin in a routine manner.

### Observation index

The following data were recorded: (I) general information for the patients, including gender and age; (II) preoperative examination findings, including measurements of the short-axis diameter of the largest left and right RLN



**Figure 1** Surgical procedure of thoracoscopic assisted tri-incisional oesophagectomy. The bilateral recurrent laryngeal nerve lymph nodes and surrounding fatty tissues were removed carefully (A,B). Subcarinal lymph nodes were removed thoroughly (C). The width of the gastric tube was 3–4 cm (D) and we had vertical mattress suture for the gastric stump to prevent esophageal diverticularization (E,F).

LN, maximum diameter of the tumour and the tumour location as determined by gastroscopy and CT, with the short-axis diameter of the largest left and right RLN LNs divided into 2 groups by cut-off points of 5 mm (14,15); and (III) intraoperative pathological data, including the degree of differentiation, subcarinal LN (SLN) status, paraoesophageal LN (PLN) status, left and right RLN LN status and total number of resected LNs. Patient and operative characteristics were collected from the medical records, and all pathological characteristics were obtained from the final pathology reports completed by two professional pathologists.

This study was reviewed and approved by the Ethics Committee of the General Hospital of the Jinan Military

Area (JN2018012) and the Second Affiliated Hospital of Shandong University (SD20180131). All patients provided written informed consent for their procedures.

### Statistical analysis

Statistical analysis was performed with SPSS 19.0 software (SPSS Inc., Chicago, Illinois, USA). Measurement data conforming to a normal distribution are described as the mean  $\pm$  standard deviation. The risk factors for RLN LN metastasis included deviation. The Levene test was used to judge the homogeneity of variance. Independent sample *t*-tests (two-sided) were used for inter-group comparisons. Numerical data are expressed in terms of frequencies and

percentages and were compared by the Pearson  $\chi^2$  test (two-sided); Fisher's exact test was used when the expected frequencies of one or more cells were less than 5. The risk factors for RLN LN metastasis were analysed by univariate analysis, and variables with a P value <0.1 were entered into multivariate logistic regression to formulate a model for predicting RLN LN metastasis. The Hosmer-Lemeshow goodness of fit test and the area under receiver operator characteristic (ROC) curve (AUC) were calculated to evaluate the model. By using R software, we constructed the nomogram according to the results of the logistic regression analysis.

## Results (Figures 2-4)

### *Postoperative complications and lymphatic dissection*

There were 265 patients who matched the conditions above, of which 222 (83.8%) were males, and 43 (16.2%) were females, aged from 41 to 68 years old [95% confidence interval (CI): 63.03±1.00]. A total of 258 patients (97.4%) underwent R0 resection, and 7 underwent R1 resection. The overall 30-day mortality rate was 2.3%. Two patients died from aortic rupture, and 2 died from respiratory failure, which resulted in an operation-specific 30-day mortality rate of 1.5%. Postoperative complications occurred in 53 (20.0%) patients. Notably, 13.6% of the patients experienced RLN injuries, of which 19.4% were bilateral.

A total of 6,255 LNs were resected from 265 patients, with 23.60±1.04 [7–58] LNs dissected per patient. The average number of left RLN LNs was 2.34±0.33 [0–16], and the metastatic rate was 15.1%. For the right RLN LNs, the average number of LNs dissected and the metastatic rate were 2.94±0.31 [0–17] and 20.4%, respectively. The total rate of RLN LN metastasis was 28.3%.

### *Analysis of RLN LN metastasis*

#### **Univariate and multivariate analysis of RLN LN metastasis**

Univariate analysis (*Table 1*) showed that risk factors for RLN LN metastasis included the short-axis diameter of the left RLN LN, the short-axis diameter of the right RLN LN, maximum tumour diameter, tumour location, SLN status and PLN status. Multivariate logistic regression analysis (*Table 2*) showed that all six variables listed above were independent predictive factors of RLN LN metastasis.

#### **Evaluation of the fit of the regression model and construction of the nomogram**

The Hosmer-Lemeshow test calculated that  $\chi^2=4.901$ ,  $P=0.768$ . A ROC curve was constructed according to the regression model (*Figure 2A*), and the area under the ROC curve (AUC) was 0.809 (95% CI: 0.754–0.864). When a predictive probability =0.143 was used as the cut-off value, the sensitivity and specificity of the nomogram for predicting RLN LN metastasis were 94.7% and 43.7%, respectively. The nomogram (*Figure 3*) constructed according to the regression model included the following six variables: short-axis diameter of the left RLN LN, short-axis diameter of the right RLN LN, maximum tumour diameter, tumour location, SLN status and PLN status.

### *Analysis of right RLN LN metastasis alone*

#### **Multivariate analysis of right RLN LN metastasis alone**

Univariate analysis (*Table 1*) showed that risk factors for right RLN LN metastasis included the short-axis diameter of the left RLN LN, short-axis diameter of the right RLN LN, maximum tumour diameter, tumour location, SLN status and PLN status. Multivariate logistic regression analysis (*Table 3*) showed that short-axis diameter of the right RLN LN, tumour location, and SLN status were independent predictive factors of right RLN LN metastasis.

#### **Evaluation of the fit of the regression model and construction of the nomogram**

The Hosmer-Lemeshow test calculated that  $\chi^2=1.735$ ,  $P=0.988$ . A ROC curve was constructed according to the regression model (*Figure 2B*), and the AUC was 0.868 (95% CI: 0.815–0.920). When a predictive probability =0.113 was used as the cut-off value, the sensitivity and specificity of the nomogram for predicting RLN LN metastasis were 94.3% and 61.6%, respectively. The nomogram (*Figure 4*) that was constructed according to the regression model included the following three variables: short-axis diameter of the right RLN LN, tumour location and SLN status.

### *Analysis of left RLN LN metastasis alone*

#### **Multivariate analysis of left RLN LN metastasis alone**

Univariate analysis (*Table 1*) showed that risk factors for left RLN LN metastasis included the short-axis diameter of the left RLN LN, maximum tumour diameter, SLN status

**Table 1** Univariate analysis of RLN LN metastasis and the right or left RLN LN metastasis alone

Risk factors	Negative	RLN LN metastasis			Left RLN LN metastasis alone			Right RLN LN metastasis alone		
		Positive	t or $\chi^2$	P value	Positive	t or $\chi^2$	P value	Positive	t or $\chi^2$	P value
Age (years)	62.96±1.13	63.11±2.11	-0.126	0.900	64.95±4.64	-0.817	0.423	61.11±2.41	1.281	0.202
Sex (n)			0.187	0.665		0.065	0.799		1.539	0.215
Male	158	64			17			32		
Female	32	11			4			3		
Tumor location (n)			9.129	0.010		0.461	0.794		9.496	0.009
Upper	17	16			2			9		
Middle	77	32			10			15		
Lower	96	27			9			11		
Degree of differentiation (n)			2.482	0.289		0.027	0.987		1.889	0.389
Well	19	7			2			3		
Moderately	102	33			11			15		
Poorly	69	35			8			17		
Maximum diameter of tumor (mm)	3.936±0.216	4.692±0.313	-3.733	0.000	4.800±0.472	-2.526	0.012	4.489±0.530	-1.957	0.052
Short axis diameter of left RLN LN			16.091	0.000		14.719	0.000		4.068	0.044
<5 mm	158	45			10			24		
≥5 mm	32	30			11			11		
Short axis diameter of right RLN LN			25.450	0.000		0.865	0.352		36.290	0.000
<5 mm	116	20			15			2		
≥5 mm	74	55			6			33		
SLN status			21.524	0.000		6.977	0.008		18.749	0.000
Negative	177	54			16			24		
Positive	13	21			5			11		
PLN status			16.580	0.000		10.612	0.001		8.080	0.004
Negative	151	41			10			20		
Positive	39	34			11			15		

RLN LN, recurrent laryngeal nerve lymph node; SLN, subcarinal lymph node status; PLN, paraoesophageal lymph node status.

and PLN status. Multivariate logistic regression analysis (Table 4) showed that the short-axis diameter of the left RLN LN was an independent risk factor for left RLN LN metastasis alone. We did not construct a nomogram, as there was only one independent risk factor from the available data.

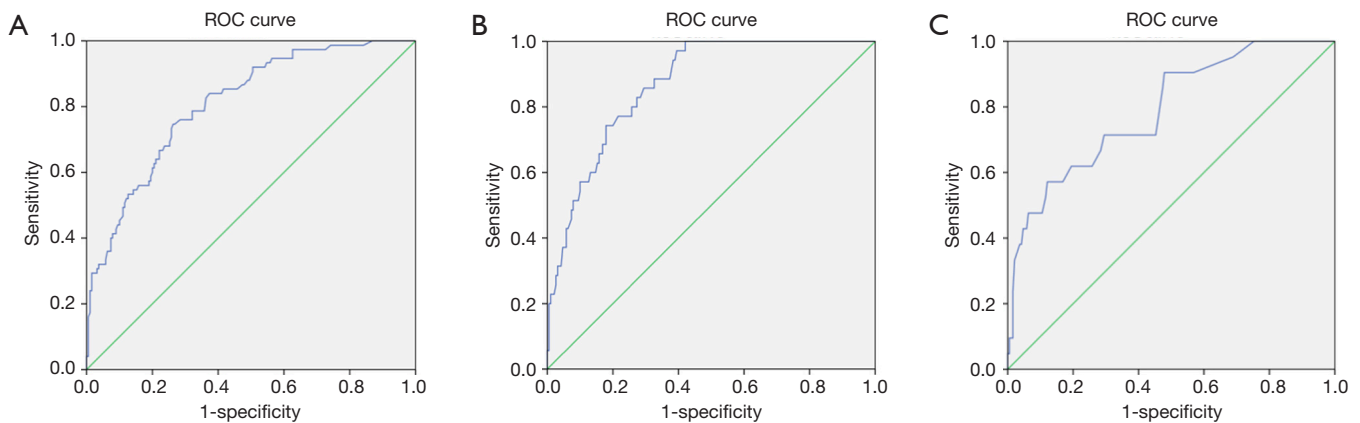
#### Evaluation of the fit of the regression model for left RLN LN metastasis alone

The Hosmer-Lemeshow test calculated that  $\chi^2=6.273$ ,  $P=0.617$ . The AUC value calculated from the left RLN LN metastasis alone (Figure 2C) was 0.790 (95% CI: 0.688–0.892). When a predictive probability =0.036 was used

**Table 2** Multivariate logistic regression analysis of the RLN LNs metastasis (n=265)

Risk factors	B	P value	OR value (95% CI)
Tumor location		0.019	
Upper vs. lower	1.391	0.005	4.017 (1.526–10.573)
Middle vs. lower	0.388	0.278	1.474 (0.731–2.971)
Maximum diameter of the tumor	0.214	0.047	1.238 (1.003–1.530)
SLN (positive vs. negative)	1.441	0.001	4.225 (1.756–10.165)
PLN (positive vs. negative)	0.834	0.020	2.302 (1.140–4.647)
Short axis diameter of left RLN LN	0.893	0.012	2.443 (1.218–4.899)
Short axis diameter of right RLN LN	1.224	0.000	3.401 (1.771–6.531)
Constant term	-3.630	0.000	0.027

RLN LN, recurrent laryngeal nerve lymph node; SLN, subcarinal lymph node status; PLN, paraoesophageal lymph node status; CI, confidence interval; OR, odds ratio; B, regression coefficient.



**Figure 2** ROC curve according to the regression model of the recurrent laryngeal nerve lymph node metastasis (A), the right recurrent laryngeal nerve lymph node metastasis (B) and the left recurrent laryngeal nerve lymph nodes metastasis alone (C). The area under ROC curve is 0.809, 0.868 and 0.790, respectively. ROC, receiver operator characteristic.

as the cut-off value, the sensitivity and specificity of the logistic model for predicting left RLN LN metastasis alone were 95.2% and 31.1%, respectively.

## Discussion

Locoregional LN recurrence is the main factor affecting the prognosis of ESCC patients postoperatively (4,16). LNs near the bilateral RLN are one of the most common locations of local recurrence. More importantly, RLN LN metastasis has been shown to be a strong predictor of poor prognosis in thoracic ESCC patients (17-19). Tabira *et al.* (18) reported that the 5-year survival rate of patients with RLN

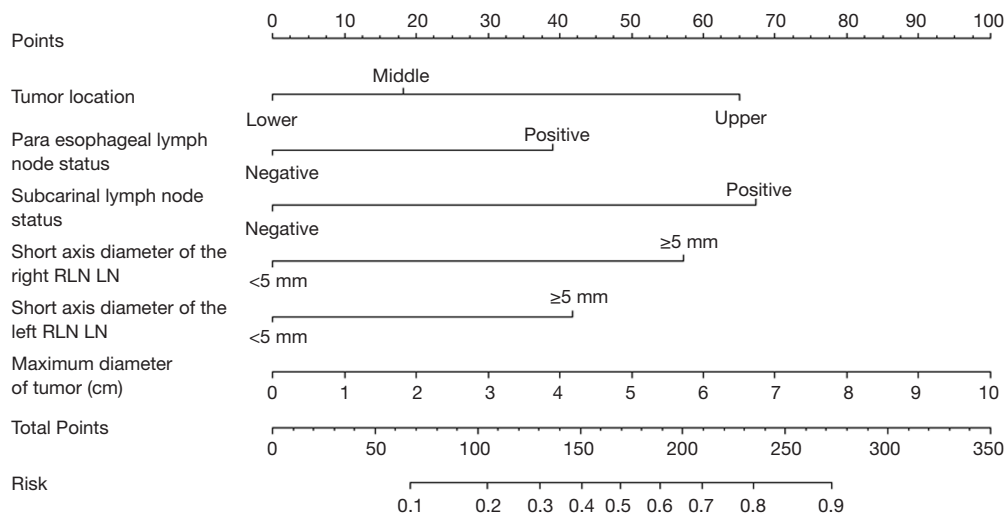
LN metastasis was 21%, which was significantly lower than that of patients with no RLN LN metastasis (47%). Some experts have considered that regular RLN LN dissection is necessary during surgery for ESCC because this process led to more precise staging and a reduction in the recurrence rate (20). Furthermore, RLN LN metastasis is an important risk factor for cervical LN metastasis (18-20). Therefore, comprehensive research should be conducted on RLN LN metastasis.

The RLN LN is one of the most common metastatic sites in oesophageal cancer, and previous research has reported that the RLN LN metastasis rate is 15–42% (19,21-23). Ye *et al.* (17) reported that the rates of left

**Table 3** Multivariate analysis of the right RLN LN metastasis alone

Risk factors	B	P value	OR value (95% CI)
SLN (positive vs. negative)	1.406	0.018	4.079 (1.278–13.016)
PLN (positive vs. negative)	0.940	0.072	2.560 (0.919–7.133)
Tumor location		0.036	
Upper vs. lower	1.709	0.010	5.522 (1.493–20.419)
Middle vs. lower	0.497	0.344	1.644 (0.587–4.602)
Short axis diameter of left RLN LN	0.406	0.437	1.501 (0.538–4.188)
Short axis diameter of right RLN LN	3.017	0.000	20.436 (4.589–91.009)
Maximum diameter of the tumor	0.088	0.529	1.092 (0.830–1.437)
Constant term	-5.378	0.000	0.005

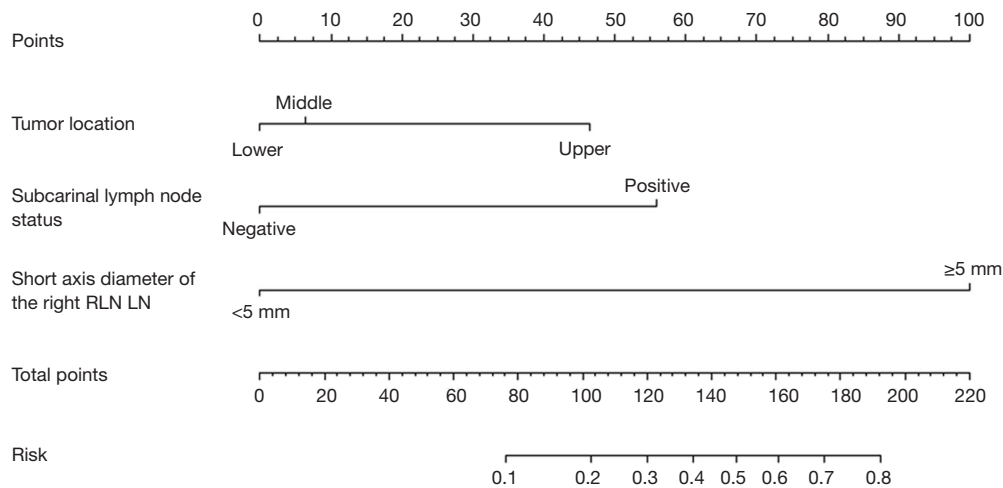
RLN LN, recurrent laryngeal nerve lymph node; SLN, subcarinal lymph node status; PLN, paraoesophageal lymph node status; CI, confidence interval; OR, odds ratio; B, regression coefficient.



**Figure 3** The nomogram model for predicting the recurrent laryngeal nerve lymph node metastasis. RLN LN, recurrent laryngeal nerve lymph node.

and right RLN LN metastasis were 15.8% and 20.8%, respectively, and Kanemura *et al.* (19) reported rates of 15.4% and 16.9%, respectively. Our research showed that the rates of left and right RLN LN metastasis were 15.10% and 20.40%, respectively, and the total metastatic rate of the bilateral RLN LNs was 28.3%, which was similar the results of a previous study. However, dissection of the RLN LNs causes the following problems. First, the procedure requires a trans-right thoracic resection of the oesophagus and lymphadenectomy and neck anastomosis, which leads to additional trauma. In addition, dissection of the LNs

along the RLNs is technically challenging for thoracic surgeons. Above all, extensive lymphadenectomy along the RLNs leads to increased complications, such as RLN injury, pulmonary infection and anastomotic fistula (12,23-25), and leads to a poor quality of life (21). Taniyama *et al.* (11) showed that 36% of patients experienced RLN injuries, of which 16% were bilateral. Ma *et al.* (24) reported that RLN palsy occurred in 37.6% of patients. In the present study, the incidence of RLN injury was 13.6%, of which 53.8% (21/39) of cases led to subsequent pulmonary infection, which was a higher rate than that observed in



**Figure 4** The nomogram model for predicting the right recurrent laryngeal nerve lymph node metastasis alone. RLN LN, recurrent laryngeal nerve lymph node.

**Table 4** Multivariate analysis of the left RLN LN metastasis alone

Risk factors	B	P value	OR value (95% CI)
Short axis diameter of left RLN LN	1.556	0.002	4.741 (1.739–12.922)
Short axis diameter of the tumor	0.243	0.137	1.275 (0.926–1.755)
SLN (positive vs. negative)	1.192	0.082	3.294 (0.859–12.630)
PLN (positive vs. negative)	0.828	0.121	2.288 (0.803–6.516)
Constant term	–4.213	0.000	0.015

RLN LN, recurrent laryngeal nerve lymph node; SLN, subcarinal lymph node status; PLN, paraoesophageal lymph node status; CI, confidence interval; OR, odds ratio; B, regression coefficient.

the group without RLN injuries (7.9%, 18/229). Hence, surgical complications may be reduced for ESCC patients if unnecessary LN dissections are avoided.

Very few studies have reported the risk factors and pattern of RLN LN metastasis (24,26). Imaging experts have used FDG-PET/CT or intravenous contrast-enhanced CT to evaluate the risk of RLN LN metastasis; however, these modalities only showed limited predictive value (19,27,28). Yu *et al.* (26) made a rough estimate of the probability of RLN LN metastasis by dividing the risks into three grades, but the values used to determine the risk factors could not be obtained preoperatively.

Our statistical results showed that the short-axis diameter of the left RLN LN, the short-axis diameter of the right RLN LN, maximum tumour diameter of the, tumour location, SLN status and PLN status were all independent risk factors for RLN LN metastasis. In this study, we did

not include T-stage in the multivariate analysis because it was unable to be determined preoperatively and had a strong linear correlation to the maximum tumour diameter. Endoscopic ultrasonography provides much information, but the accuracy is not satisfactory currently. Therefore, we did not include T-stage in our model in consideration of the clinical practicability. The data also showed that the rates of RLN LN metastasis for cases with SLN metastasis or not were 61.76% and 23.38%, respectively. Therefore, SLN status was a vital prognostic factor for RLN LN metastasis.

Finally, we formulated a logistic regression model and constructed a nomogram accordingly. The values of the abovementioned variables can be determined preoperatively or intraoperatively. For example, one patient with the lower third thoracic ESCC (0 points) underwent oesophagectomy, and the maximum diameters of the left (0 points) and right (0 points) RLN LNs were all less than 5 mm on



CT. The maximum diameter of the tumour measured intraoperatively was 4 cm (40 points), and the intraoperative pathological analysis showed that the SLN status (0 points) and PLN status (0 points) were both negative. These six values summed to 40 points. Therefore, we determined that the risk of RLN LN metastasis was less than 0.1. As shown above, the risk of RLN LN metastasis can be determined according to the scoring system. The AUC of the model was 0.809, which proved that this scoring system had a high accuracy for predicting RLN LN metastasis.

However, our study had several limitations and shortcomings. First, our study design was retrospective, and the sample size was small; thus, selection bias was unavoidable, and further multi-institutional studies with larger sample sizes need to be performed in the future. Another limitation was the absence of clinical outcomes because of the short follow-up period. We have begun to collect prognostic information regarding RLN LN metastasis.

In summary, our study showed that upper thoracic ESCC patients with larger tumours and larger RLN LNs are more prone to RLN LN metastasis. Metastasis of the subcarinal and PLNs is also closely related to RLN LN metastasis. By quantifying the risk factors described above, we formulated a scoring system to accurately estimate the risk of RLN LN metastasis. However, the accumulation of more data and prospective studies are needed in the future to further improve the model and to provide more accurate guidance for clinical treatment.

### Acknowledgments

We thank Dr. Ning Jiang for his help in collecting data (Department of Thoracic Surgery, The Second Hospital of Shandong University, Jinan, China) and Xiao Qiang and Yuan Zhang (Evidence-based Medicine Centre, The Second Hospital of Shandong University, Jinan, China) for their contributions to the statistical analysis in this article.

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* 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. This study was

reviewed and approved by the Ethics Committee of the General Hospital of the Jinan Military Area (JN2018012) and the Second Affiliated Hospital of Shandong University (SD20180131). All patients provided written informed consent for their procedures.

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**Cite this article as:** Liu Y, Zou ZQ, Xiao J, Zhang M, Yuan L, Zhao XG. A nomogram prediction model for recurrent laryngeal nerve lymph node metastasis in thoracic oesophageal squamous cell carcinoma. *J Thorac Dis* 2019;11(7):2868-2877. doi: 10.21037/jtd.2019.06.46