



Clinical evaluation of right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma

Zhen-Xuan Li^{1#}, Xiao-Dong Li^{2#}, Xian-Ben Liu¹, Wen-Qun Xing¹, Hai-Bo Sun¹, Zong-Fei Wang¹, Rui-Xiang Zhang¹, Yin Li^{1,3}

¹Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China; ²Department of Thoracic Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China; ³Department of Thoracic Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

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[#]These authors contributed equally to this work.

Correspondence to: Yin Li, MD, PhD. Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, 127 Dongming Rd, Zhengzhou 450008, China. Email: liyin825@sina.com.

Background: The accuracy of clinical N staging of esophageal squamous cell carcinoma is suboptimal. As an important station of lymph node metastasis, station C201 (right recurrent laryngeal nerve nodes) has rarely been evaluated alone. We aimed to explore an effective way to evaluate the right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma.

Methods: We retrospectively analyzed 628 thoracic esophageal squamous cell carcinoma patients who underwent radical resection without neoadjuvant therapy from two Chinese cancer centers. The diameter of the short axis of the largest right recurrent laryngeal nerve node (DC201) was measured on contrast-enhanced multi-slice computed tomography (MSCT). Right recurrent laryngeal nerve nodes were examined by postoperative pathologic results. The receiver operating characteristic (ROC) curve was generated to assess the diagnostic capabilities of DC201 to determine the right recurrent laryngeal nerve nodes status.

Results: ROC curve analysis revealed that the optimal cut-off point of DC201 was 6 mm, with an area under curve (AUC), sensitivity, specificity, and Youden index of 0.896, 71.9%, 88.8%, and 0.607 respectively. When the cut-off point of DC201 was set to 10 mm, sensitivity, specificity and the Youden index were 14.1%, 99.6% and 0.137 respectively. Among 128 patients with right recurrent laryngeal nerve node metastasis, 71 and 108 patients had the largest right recurrent laryngeal nerve node located above the suprasternal notch level and in the tracheoesophageal groove respectively.

Conclusions: When DC201 ≥ 6.0 mm instead of DC201 ≥ 10 mm was used to dictate the right recurrent laryngeal nerve nodes metastasis, contrast-enhanced MSCT could evaluate the status of right recurrent laryngeal nerve nodes with high sensitivity and specificity. The largest right recurrent laryngeal nerve nodes were mainly located in the tracheoesophageal groove and/or above the suprasternal notch.

Keywords: Esophageal squamous cell carcinoma; computed tomography (CT); diagnosis; right recurrent laryngeal nerve nodes; cancer staging

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Introduction

Clinical and pathologic categories of lymph node status for thoracic esophageal squamous cell carcinoma are not considered to denote prognostic implications by the Worldwide Esophageal Cancer Collaboration for the AJCC/UICC cancer staging manuals 8th edition (1-3). For cT1 and cT2 squamous cell carcinoma, no disparities of risk-adjusted survival were noted between cN0 and cN1, raising the possibility of low accuracy of clinical N staging (2). To our knowledge, clinical criteria for lymph node metastasis have not been established rigorously in peer-reviewed literature. In clinical practice, locoregional nodes are generally suspicious for tumor involvement when being round in shape and/or >10 mm in the short axis. However, the sizes of normal lymph nodes vary significantly in different stations (4-6), suggesting that adopting flexible criteria for lymph nodes in different stations may improve the accuracy of clinical N staging.

In the lymph node maps for esophageal cancer, right recurrent laryngeal nerve nodes (station C201) are located along the right recurrent laryngeal nerve that are superiorly and inferiorly bounded by the cephalic border of the right subclavian artery, and the caudal border of the right recurrent laryngeal nerve curving upward respectively (7), which is equivalent to right upper paratracheal nodes (station 2R) in AJCC/UICC classification (8th). Right upper paratracheal nodes are located between the intersection of the caudal margin of the brachiocephalic artery with the trachea and the apex of the lung (8), station C201 has been documented to be the most frequent site of lymph node metastases of thoracic esophageal squamous cell carcinoma (9-11). Moreover, recurrent laryngeal nerve injury that is related to station C201 dissection is a common surgical complication that is associated with aspiration pneumonia (12-15). Thus right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma are the focus of thoracic surgeons' attention. The purpose of our study is to explore whether adopting a different criterion improve the clinical diagnostic efficacy of right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-774>).

Methods

The trial was conducted in accordance with the Declaration

of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Sun Yat-sen University Cancer Center (SYSUCC) and the Affiliated Cancer Hospital of Zhengzhou University (ACHZZU). Informed consents were waived due to its retrospective nature. The electronic medical records of all patients who underwent esophagectomy with extended mediastinal lymph node dissection for thoracic esophageal squamous cell carcinoma at SYSUCC between October 2009 and September 2012, and at ACHZZU between January 2013 and December 2016 were reviewed. Patients who received neoadjuvant therapy were excluded, as were those who had other concomitant cancers and those who did not undergo a resection with curative intent. Patients with incomplete clinical or imaging data were also excluded. Data were collected from 2 different institutions at different time periods due to the work transfer of the author. Furthermore, in order to increase study reliability, we only selected patients whose surgeons performed >100 such operations per year. Data from a total of 628 patients were included into the final analysis, including 236 and 392 from SYSUCC and ACHZZU respectively. There was no difference between the two centers in the extent of dissection of right recurrent laryngeal nerve nodes. Surgeons used to open the superior mediastinal pleura along the posterior edge of the trachea, dissociate the posterior wall of the esophagus to the top of the pleura, separate the right recurrent laryngeal nerve along the right subclavian artery, and excise the right recurrent laryngeal nerve nodes together with the adipose tissue. The removed right recurrent laryngeal nerve nodes were placed in a separate container for pathological examination.

Five mm thickness contrast-enhanced multi-slice computed tomography (MSCT) of the chest and abdomen were retrieved from the Picture Archiving and Communication Systems and reviewed (In order to unify standards, we use 5 mm sliders for assessment). The radiographs were reviewed by a radiologist and a surgeon, and when the results differed, they were discussed and recorded after a consensus was reached. The largest right recurrent laryngeal nerve node in each patient was identified, followed by measurement of its short axis diameter and recoding its location. We defined $\angle\alpha$ in *Figure 1*, the line between the center of trachea and the center of esophagus is regarded as one side, and the horizontal line is regarded as the other side. Right recurrent laryngeal nerve nodes located in the tracheoesophageal groove were represent by A, Right recurrent laryngeal nerve nodes located

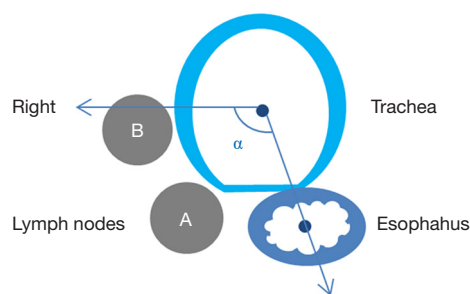


Figure 1 Distribution of metastatic right recurrent laryngeal nerve nodes on the transverse plane. A, Right recurrent laryngeal nerve nodes located in the tracheoesophageal groove; B, Right recurrent laryngeal nerve nodes located on the right side of the trachea away from the esophagus; $\angle\alpha$, The line between the center of trachea and the center of esophagus is regarded as one side, and the horizontal line is regarded as the other side.

on the right side of the trachea away from the esophagus were represented by B. Right recurrent laryngeal nerve nodes were divided into the cervical, junctional and thoracic right recurrent laryngeal nerve nodes respectively by the suprasternal notch (*Figure 2*). Postoperative pathological examinations were used as the gold standard to ascertain the right recurrent laryngeal nerve nodes status. The distances between the lymph nodes and the incisors were retrieved from patients at SYSUCC who routinely underwent endoscopic ultrasonography (EUS). We set the lower boundary of right recurrent laryngeal nerve nodes as 23 cm from the incisors.

Numerical data were expressed as mean \pm standard deviation or median for randomly and non-randomly distributed data respectively. Categorical variables were presented as frequencies or ratios, as appropriate. The chi-square or Fisher exact tests were applied to analyze

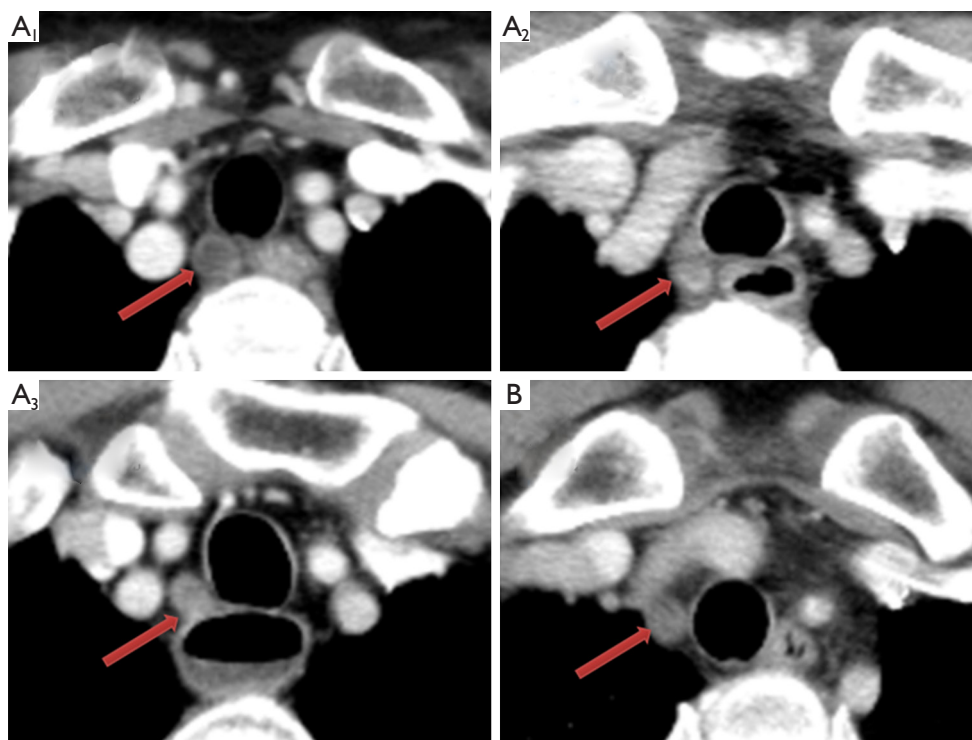


Figure 2 Distribution of metastatic right recurrent laryngeal nerve nodes on contrast-enhanced MSCT. A1, cervical right recurrent laryngeal nerve nodes in the tracheoesophageal groove; A2, junctional right recurrent laryngeal nerve nodes in the tracheoesophageal groove; A3, thoracic right recurrent laryngeal nerve nodes in the tracheoesophageal groove; B, right recurrent laryngeal nerve nodes located on the right side of the trachea away from the esophagus. MSCT, multi-slice computed tomography.

Table 1 Characteristics of patients with and without Right recurrent laryngeal nerve nodes metastasis

Characteristic	No. of patients (RRLNN-), n (%)	No. of patients (RRLNN+), n (%)	P value
Sex			0.277
Male	363 (5.7)	99 (15.8)	
Female	137 (21.8)	29 (4.6)	
Tumor location			0.003
Upper	116 (18.5)	48 (7.6)	
Middle	243 (38.9)	55 (8.8)	
Lower	141 (22.5)	25 (4.0)	
Tumor depth			0.001
pTis	20 (3.2)	0 (0.0)	
pT1a	48 (7.6)	2 (0.3)	
pT1b	83 (13.2)	16 (2.5)	
pT2	126 (20.1)	33 (5.3)	
pT3-4a	223 (35.5)	77 (12.3)	
Histologic grade [†]			0.727
G1	49 (7.8)	12 (1.9)	
G2	198 (31.5)	56 (8.9)	
G3	183 (29.1)	58 (9.2)	

[†], 72 patients with GX were excluded. RRLNN-, right recurrent laryngeal nerve node negative; RRLNN+, right recurrent laryngeal nerve node positive.

differences among the categorical data. Receiver-operating characteristic (ROC) curve was constructed to calculate the area under the curve (AUC), specificity and sensitivity. The diameter of the short axis of the largest right recurrent laryngeal nerve node (DC201) was used as the test variable, and the pathological result of right recurrent laryngeal nerve node was used as the state variable. Youden index (sensitivity + specificity - 1) was used to determine the optimal cut-off point. A two-sided P value <0.05 was considered to be statistically significant.

Results

The lymph node ratio of station C201 was higher than that of other stations

Patient characteristics are shown in *Table 1*. The median age was 60 years (range, 38–85 years). The proportions of stage pN0, pN1, pN2 and pN3 patients were 56.8%, 26.3%, 13.7% and 3.2%, respectively. A total of 19062 lymph nodes were dissected, with an average of 30.4±14.4 lymph

nodes per case, including 1878 right recurrent laryngeal nerve nodes, with an average of 3.0±2.4 lymph nodes. A total of 750 metastatic lymph nodes were dissected, including 199 metastatic right recurrent laryngeal nerve nodes. The lymph node ratio is defined as the total number of dissected nodes divided by the number of metastatic nodes. The lymph node ratio of right recurrent laryngeal nerve nodes, paracardial nodes, paraesophageal lymph nodes, left recurrent laryngeal nerve nodes, left gastric nodes, subcarinal nodes and diaphragmatic nodes were all greater than 1%. The lymph node ratio was 10.6%, 5.0%, 4.9%, 4.4%, 4.2%, 2.5% and 1.0%, respectively. The lymph node ratio of station C201 was significantly higher than that of lymph nodes in other stations (10.6% vs. 3.2%, P<0.001).

Tumor location and tumor depth are related to right recurrent laryngeal nerve node metastasis

The correlation between gender, tumor location, tumor depth, histologic grade and lymph nodes was shown in

Table 1. Right recurrent laryngeal nerve node metastasis rate of upper thoracic esophageal squamous cell carcinoma was higher than that of middle and lower thoracic esophageal squamous cell carcinoma ($P=0.003$). Right recurrent laryngeal nerve node metastasis was rare in patients with pT1a, but more in patients with pT1b, pT2, pT3 and pT4a. There was no statistically significant difference with regard to the right recurrent laryngeal nerve node metastasis rate between patients with pT1b, pT2 and pT3 ($P=0.145$), nor between patients with middle thoracic and lower thoracic esophageal squamous cell carcinoma ($P=0.353$).

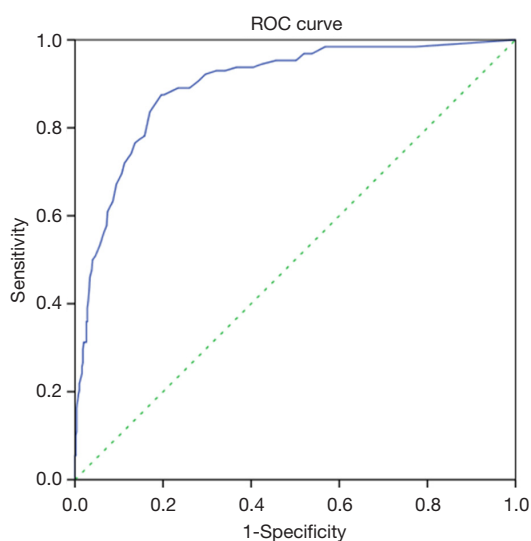


Figure 3 ROC curve for right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma. ROC, receiver operating characteristic.

This suggests that upper thoracic esophageal tumor and tumor breakthrough of submucosa are risk factors for right recurrent laryngeal nerve node metastasis in thoracic esophageal squamous cell carcinoma.

The detection rate of right recurrent laryngeal nerve node metastasis by EUS was only 33.3%

Of all the 236 patients from SYSUCC who attempted EUS, 36 failed to complete EUS due to esophageal stenosis ($n=35$) or suspected esophageal perforation ($n=1$). Among those who successfully completed EUS, 54 had right recurrent laryngeal nerve node metastasis, among which only 18 were found to have lymph nodes within 23 cm from the incisors.

The optimal cut-off point of DC201 was 5.4 mm instead of 10 mm

Of the 628 patients enrolled, 128 had right recurrent laryngeal nerve node metastases. ROC curve analysis revealed that the optimal cut-off point of DC201 was 5.4 mm, with AUC of 0.896 (Figure 3), sensitivity of 87.5%, specificity of 80.4%, accuracy of 81.8%, and the Youden index of 0.679. When the cut-off point of DC201 was set to 10.0 mm, sensitivity, specificity, accuracy and the Youden index were 14.1%, 99.6%, 82.2%, and 0.137 respectively. The diagnostic capabilities of DC201 at different cut-off points were summarized in Table 2. We observed that the probability of right recurrent laryngeal nerve node metastasis was 3.2% (12/372) when DC201 <5 mm, but it increased to 45.3% (116/256) when DC201 \geq 5 mm.

Table 2 Diagnostic efficacy of DC201 with different cut-off points

Cut-off point, mm	Sensitivity (%)	Specificity (%)	Accuracy (%)	YI
4	96.9 (124/128)	48.0 (240/500)	58.0 (364/628)	0.449
5	90.6 (116/128)	72.0 (360/500)	74.4 (476/628)	0.626
5.4	87.5 (112/128)	80.4 (402/500)	81.8 (514/628)	0.679
6	71.9 (92/128)	88.8 (444/500)	85.4 (536/628)	0.607
7	50.0 (64/128)	96.0 (480/500)	86.6 (544/628)	0.460
8	31.3 (40/128)	97.4 (487/500)	83.9 (527/628)	0.287
9	21.1 (27/128)	99.0 (495/500)	83.1 (522/628)	0.201
10	14.1 (18/128)	99.6 (498/500)	82.2 (516/628)	0.137

DC201, the diameter of the short axis of the largest right recurrent laryngeal nerve node; YI, Youden Index.

The largest right recurrent laryngeal nerve nodes were mainly located in the tracheoesophageal groove and/or above the suprasternal notch

The anatomical distribution of the largest right recurrent laryngeal nerve nodes in 128 patients with right recurrent laryngeal nerve node metastasis was also analyzed. Two patients were further excluded since their right recurrent laryngeal nerve nodes were too small to be clearly visualized even on contrast-enhanced MSCT. The number of cervical, junctional and thoracic maximal right recurrent laryngeal nerve nodes was 71, 20 and 35, respectively. On the transverse plane, the largest right recurrent laryngeal nerve nodes were located within $\angle\alpha$ in 124 patients (Figure 1), 108 of which were located in the tracheoesophageal groove (Figure 2).

Discussion

Esophageal lymphatic vessels run longitudinally in the lamina propria and the submucosa and circumferentially in the intermuscular space (16,17). The longitudinal submucosal lymphatic network run along the right tracheoesophageal groove and is continuous with the lymphatics of the pharynx and the stomach (18). Only the right recurrent laryngeal nerve nodes have been previously extensively investigated and confirmed to be connected directly to the submucosal lymphatic plexus (16,18). This anatomic structure underlies why right recurrent laryngeal nerve nodes have a higher rate of metastasis in thoracic esophageal squamous cell carcinoma. In line with this, our finding corroborated that the lymph node ratio of station C201 was significantly higher than that of lymph nodes in other stations.

The accuracy of clinical diagnosis of lymph nodes in esophageal cancer remains suboptimal (2,19,20). Chest and abdominal CT scan with intravenous contrast and fluorine-18-fluoro-2-deoxy-D-glucose positron emission tomography (PET)/CT imaging are commonly employed imaging modalities to evaluate lymph nodes status. Unfortunately, CT and PET/CT imaging are curtailed by their low accuracy for detecting lymph node metastasis (21-27). Although recent developments in magnetic resonance (MR) imaging techniques have resulted in improved imaging quality and diagnostic accuracy of lymph node metastasis (28-30), this modality is seldomly used for the staging of patients with esophageal cancer. EUS has been shown to be superior to CT in detecting lymph

node metastases, but the sensitivity and specificity vary dramatically depending on anatomic location (22,31,32). In this study, the detection rate of right recurrent laryngeal nerve node metastasis by EUS was only 33.3%, which is congruent with a prior study by Shan *et al.* that reported a sensitivity of merely 32.4% of EUS for the evaluation of right recurrent laryngeal nerve node metastasis (33). There are mainly 3 reasons accounting for this poor sensitivity. First, right recurrent laryngeal nerve nodes are obscured by the trachea in a subset of cases (more than 12.5% in our study). Second, right recurrent laryngeal nerve nodes are relatively smaller than those in other stations, so they are prone to be missed by EUS. Finally, the accuracy of EUS was also influenced by operator experience. Among the 54 patients who underwent EUS examination and had right recurrent laryngeal nerve nodes metastasis, 46 patients had DC201 ≥ 5.4 mm, accounting for 85.2%. It is obvious that under the new standard, MSCT is better than EUS in detecting right recurrent laryngeal nerve nodes. Due to the high cost of PET/CT examination and its mediocre performance in clinical N staging, it is rarely used in the evaluation of operable patients, so we do not have reliable data on PET/CT in this group of patients.

In clinical practice, regional lymph nodes are only suspicious for tumor involvement when being round in shape and/or >10 mm in short axis diameter. This may underscore the notoriously poor accuracy of CT in diagnosing lymph node metastasis. As illustrated in the present study, the sensitivity of CT in diagnosing right recurrent laryngeal nerve node metastasis was only 14.1% when short axis diameter ≥ 10 mm was adopted as the criteria for tumor involvement. However, ROC curve indicated a good correlation between right recurrent laryngeal nerve node metastasis and DC201. When DC201 ≥ 5.4 mm was applied to define metastasis, the sensitivity, specificity and accuracy improved dramatically. We also analyzed data from SYSUCC and ACHZZU separately, and their AUC, optimal cut-off point, sensitivity and specificity was 0.851, 5.2 mm, 87.5%, 72.1% and 0.927, 5.5 mm, 87.5%, 80.4% respectively. This minor difference could potentially be explained by the fact that a larger percentage of patients at ACHZZU were excluded because of neoadjuvant therapy. The sensitivity and specificity of different cut-off points are listed in Table 2. We found that the sensitivity was 96.9% when the cut-off point was 4 mm, and the specificity was 96.0% when the cut-off point was 7 mm. This suggests that in clinical practice, if we find DC201 <4 mm, we can consider it as negative right recurrent laryngeal nerve node;

if we find $DC201 \geq 7$ mm, we can consider it as positive right recurrent laryngeal nerve node.

Fine-needle aspiration [FNA] could aid in improving the sensitivity and specificity of EUS in evaluating N stage disease (34). Lymph nodes with suspected metastasis can be identified by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) (33,35). However, under what conditions lymph node biopsies are the best approach to be recommended? We observed that the probability of right recurrent laryngeal nerve node metastasis was minimal (3.2%) when $DC201 < 5$ mm, whereas it increased to 45.3% when $DC201 \geq 5$ mm. Therefore, we suggest that EUS-FNA or EBUS-TBNA examination should be used to further clarify the status of right recurrent laryngeal nerve node when $DC201 \geq 5$ mm.

Station C201 in Chinese system and Station 2R in AJCC/UICC system are similar but different. We found that almost all the right recurrent laryngeal nerve nodes were distributed in $\angle \alpha$ (Figure 1), which suggested that Station C201 could better reflect the distribution of lymph nodes in this region than Station 2R. It also suggests that there is no need to dissect the anterior right side of the trachea to reduce the risk of right recurrent laryngeal nerve injury and right subclavian artery bleeding. Right recurrent laryngeal nerve nodes located in the tracheoesophageal groove were represent by A, Right recurrent laryngeal nerve nodes located on the right side of the trachea away from the esophagus were represent by B. Figures 1,2 clearly show that due to tracheal obstruction, B cannot be detected during EUS examination, which is the limitation of EUS. By analyzing the proportions of A1, A2 and A3, we found that right recurrent laryngeal nerve nodes were mainly located above the suprasternal notch, which suggested that we should not omit the right recurrent laryngeal nerve nodes above the suprasternal notch due to the difficulty in the operation.

The findings of the present study must be interpreted in acknowledging its limitations. First, this was a retrospective study, since all the removed right recurrent laryngeal nerve nodes were placed in a separate container for pathological examination, we knew how many right recurrent laryngeal nerve nodes were dissected and how many were metastatic in each patient, but we did not know which lymph nodes were metastatic, so we used $DC201$ as a predictor of right recurrent laryngeal nerve nodes status. Second, due to the lack of PET/CT data, the diagnostic efficacy of PET/CT in the right recurrent laryngeal nerve lymph nodes

of thoracic esophageal squamous cell carcinoma cannot be determined in this study. In a recent meta-analysis, the sensitivity of PET/CT in diagnosing esophageal squamous cell carcinoma lymph nodes was only 66%, because small regional metastatic lymph nodes (range, 2–8 mm) could not be detected by FDG-PET in cases of esophageal carcinoma (21-27). In view of the small size of right recurrent laryngeal nerve nodes in esophageal squamous cell carcinoma, we predicted that PET/CT would not have a significant advantage over CT in the diagnosis of right recurrent laryngeal nerve nodes. Last, there is the potential for a significant bias in this study because many patients who had obvious locoregional metastases underwent neoadjuvant treatment and were excluded from this study. Therefore, we suggest that $DC201 \geq 6$ mm should replace $DC201 \geq 5.4$ mm as the diagnostic criterion for positive right recurrent laryngeal nerve nodes, so as to make up for the bias of this study.

In conclusion, we found that the diagnostic efficacy of contrast-enhanced MSCT to evaluate right recurrent laryngeal nerve node status with a criterion of $DC201 \geq 6.0$ mm was significantly higher than that when $DC201 \geq 10$ mm was set as the criteria. Additional prospective studies are needed to conclusively confirm our results.

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Footnote

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Data Sharing Statement: Available at <http://dx.doi.org/10.21037/jtd-20-774>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-774>). 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. The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Sun Yat-sen University Cancer Center and the Affiliated Cancer Hospital of Zhengzhou University. The approval number is waived because of the retrospective nature of the study. Informed consents were waived due to its retrospective nature.

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