Peer review file

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Reviewer A

This study explored an effective way to evaluate the right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma. The diameter of the short axis of the largest right recurrent laryngeal nerve node (DSALRRLNN) was measured on contrast-enhanced multi-slice computed tomography. When DSALRRLNN≥5.4mm 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.

There are several points to be addressed.

Comment 1: This method and conclusion were quite confusing. This study did not evaluate sensitivity and specificity of detecting metastatic nodes, but detecting patients with node metastasis. When the diameter of the short axis of the right recurrent laryngeal nerve node was ≥5.4mm, that node was not estimated to be metastatic or not. The diameter of the short axis of the right recurrent laryngeal nerve node ≥5.4mm is not useful for evaluating each node and counting the number of metastatic nodes.

Reply 1: 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. Since the size of the short diameter of the lymph node is strongly correlated with whether it is invaded or not, we used DC201 as a predictor of right recurrent laryngeal nerve nodes status.

Changes in the text: Line 260-261

Comment 2: As the cut-off point, 5.4mm, not 5mm nor 6mm, is not convenient for clinical use.

Reply 2: Thank you very much for your suggestion. We have made modifications in the article.

Changes in the text: Line34, 272-276

Comment 3: Metastatic right recurrent laryngeal nerve nodes were mainly located in the tracheoesophageal groove and/or above the suprasternal notch. However, as pointed above, the diameter of the short axis of the right recurrent laryngeal nerve node ≥5.4mm was not used for evaluating each node. So, each node ≥5.4mm located in the tracheoesophageal groove and/or above the suprasternal notch was not estimated as metastatic or not. So, descriptions about locations of metastatic nodes had no bases on data of locations.

Reply 3: Thanks for your reminding. The largest right recurrent laryngeal nerve node is not equivalent to metastatic right recurrent laryngeal nerve nodes. We have made modifications in the article.

Changes in the text: Line43-44, 175

Comment 4: The authors defined ∠α: 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. There was no description about clinical use of ∠α. The authors might be defined that the center of the right recurrent laryngeal nerve node that located in ∠α as in the tracheoesophageal groove.

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. The definitions of two locations were not described.

Reply 4: Thanks for your reminding.

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 ∠α(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. Figure 1 and figure 2 clearly show that due to

tracheal obstruction, B cannot be detected during EUS examination, which is the limitation of EUS.

Changes in the text: Line246-258

Comment 5: The description and data about EUS had no meaning in this study.

Reply 5: The significance of EUS data is to remind us that EUS has no advantage over CT in the diagnosis of right recurrent laryngeal nerve nodes.

Comment 6: The description and Table1 data about two institutions had no meaning. Table 4 should be Table 1. Table 3 should be Table 2. Table 2 should be Table 3. The description in Results should be changed according to Tables.

Reply 6: Thank you very much for your suggestion. We have made modifications in the article.

Comment 7: Author names in References should not be abbreviated.

Reply 7: Thank you very much for your suggestion. We have made modifications in the article.

Changes in the text: Line207

Reviewer B

The authors have performed a retrospective review of over 600 patients who underwent esophagectomy for squamous cell cancer of the esophagus. Their objective was to determine the ability of the diameter of right recurrent laryngeal lymph nodes to predict metastasis in that node.

Comment 1: It is intuitive and understandable that as the diameter cutoff is increased, the sensitivity will decrease but the specificity will increase. What is the relevance of these findings, however? Do the authors feel that if the right recurrent lymph node is greater than 5.4 mm on CT scan that it should be assumed to be positive? Or should it be 10 mm, where the specificity was over 99%?

Reply 1: You raised a very good question. 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 4mm, and the specificity was 96.0% when the cut-off point was

7mm.This suggests that in clinical practice, if we find DC201<4mm, we can consider it as negative right recurrent laryngeal nerve node; if we find DC201≥7mm, we can consider it as positive right recurrent laryngeal nerve node.

Changes in the text: Line231-236

Comment 2: Related to the first question, the authors claim that the optimal cut-off point for diameter is 5.4 mm. But the specificity is only 80% at this diameter. Is this an acceptable number? In a busy practice using this methodology, many patients would be incorrectly assumed to have metastatic disease when instead they have a false positive CT scan.

Reply 2: We suggests that in clinical practice, if we find DC201<4mm, we can consider it as negative right recurrent laryngeal nerve node; if we find DC201≥7mm, we can consider it as positive right recurrent laryngeal nerve node; if we find 4mm≤DC201<7mm, we can use other tests (EUS-FNA or EBUS-TBNA) to determine.

Changes in the text: Line234-236

Comment 3: This study looks at CT scan in an isolated fashion, but in clinical practice other modalities will be available. When we evaluate our patients for esophageal resection, PET-CT scan and EUS results are used in conjunction with CT scan findings. But the authors have looked at CT and EUS findings in isolation. As an example, the authors state that the detection rate of EUS was only 33%. 54 patients ultimately had right recurrent lymph node metastasis, but only 18 were deemed positive by EUS. But what were the CT scan characteristics in those 54 patients? What were the PET-CT scan results in those 54 patients? Is it possible to create a better predictive model by utilizing all of these studies, as opposed to using just one diagnostic test alone?

Reply 3: Among the 54 patients who underwent EUS examination and had right recurrent laryngeal nerve nodes metastasis, 46 patients had DC201≥5.4mm, 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.

Changes in the text: Line213-219

Comment 4: 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. So this study is really analyzing a very selected group, and not truly analyzing the performance of CT scan in a representative group of patients with esophageal cancer.

Reply 4: Thanks for your reminding. 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≥6mm should replace DC201≥5.4mm as the diagnostic criterion for positive right recurrent laryngeal nerve nodes, so as to make up for the bias of this study.

Changes in the text: Line272-276

Reviewer C

In the current study, author's purpose was to explore whether adopting a different criterion improve the clinical diagnostic efficacy of right recurrent laryngeal nerve nodes in thoracic esophageal squamous cell carcinoma.

However, there were several critical points to be corrected to meet the criteria of this journal. Therefore, the current study unfortunately does not meet the criteria for publishing in this journal at this point.

Major Query

Comment 1: The authors should present the basis for the data described in the text should be indicated in the table.

i. The reviewers were interested in the detail data of the lymph node ratio by other stations. And the authors need to analyze the lymph node ratio of C201 in comparison with each of the other stations.

ii. The reviewers think that the relationship between tumor location and tumor depth should be presented according to lymph node metastasis.

Reply 1: The lymph node ratio of right recurrent laryngeal nerve nodes, paracadial 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).

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.

Changes in the text: Line137-141,154-156

Comment 2: The reviewers do not find significance of dividing A1-3 and B, and of ∠α. The author should describe clinical significance of A1-3 and B or ∠α.

Reply 2: 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 ∠α(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. Figure 1 and figure 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.

Changes in the text: Line246-258

Comment 3: The authors should describe more detail about the accuracy of metastatic lymph nodes by EUS.

Reply 3: Among the 54 patients who underwent EUS examination and had right recurrent laryngeal nerve nodes metastasis, 46 patients had DC201≥5.4mm, accounting for 85.2%. It is obvious that under the new standard, MSCT is better than EUS in detecting right recurrent laryngeal nerve nodes.

Changes in the text: Line213-216

Comment 4: Although the cutoff value of DSALRRLNN was set at 5.4 mm, reviewers thought that it would not make sense to underwent EUS-FNA or EBUS-TBNA on lymph nodes larger than 5 mm.

Reply 4: Thank you very much for your suggestion. We have made modifications in the article.

Changes in the text: Line243-245

Comment 5: The abbreviation as DSALRRLNN is too long.

Reply 5: Thank you very much for your suggestion. We've substituted DC201 for DSALRRLNN

Changes in the text: Line29-30

Comment 6: Tables 2 and 3 were almost identical, and these table should be simplified.

Reply 6: Thank you very much for your suggestion. We have deleted Table 3.

Comment 7: Minor Query

1. When using abbreviations such as SYSUCC and ACHZZU, the authors should describe the official names.
2. Please arrange Figure 1 and Figure 2 in order.

Reply 7: Thank you very much for your suggestion. We have already modified it in the article.

Changes in the text: Line81-82

Reviewer D

A retrospective study on radiological diagnosis of thoracic esophageal scc-related right recurrent nerve lymph node metastases conducted by very high-volume surgeons in two centers (one with inclusion of 2009-2012 and the other with inclusion during 2013-2016).

The study is indeed interesting, and has clinical relevance for more careful characterization of lymph node metastases in esophageal squamous cell carcinoma.

However, some limitations exist.

Comment 1: The two centers had completely different inclusion periods with no overlap. It is therefore recommended to include year of surgery, as well as center, as confounders in the analyses. Another way of treating this could have been using one center as a training cohort, and the other as validation cohort to strengthen the study. The limitations related to inclusion periods in the centers are recommended to discuss in the paper.

Reply 1: Thank you very much for your suggestion. The setting of the training cohort and the validation cohort is a good way to solve the confounders. Considering the problem of sample size, we did not do so, but compared the data of the two centers in the discussion section, and found that the results of the two centers were similar.

Changes in the text: Line227-231

Comment 2: Surgical technique needs to be described in the methods and discussed, including preoperative treatment, surgical details and postoperative management, and whether there were differences between the centers or any changes in the treatment of these patients over time.

Reply 2: Thanks for your reminding. We have explained this in the article.

Changes in the text: Line93-99

Comment 3: How was it ensured that C201 lymph nodes were extracted where indicated, were these kept always separately in separate containers?

Reply 3: Thanks for your reminding. We have explained this in the article. 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.

Changes in the text: Line93-99

Comment 4: 5mm slices were used for the assessment of lymph nodes, and measurements were (supposedly) made with 0,1 or 0,2 mm accuracy. Why not use 0,5mm slides for assessment, which are routinely included at least in our department? This should be discussed.

Reply 4: In order to unify the standards of different CT machines, we use 5mm sliders for assessment. If all of them are examined with the best CT, the results may be better.

Changes in the text: Line102

Comment 5: Minor:

-Row 53: apex of the lung, station C201 has been documented to be the most frequent site of thoracic ... . It is recommended to add that it is the most frequent site of lymph node metastases of thoracic escc.

-Another abbreviation instead of DSALRRLNN is recommended, as this is a very long abbreviation and hard to remember

-Table 4 needs reporting of percentages, as in other tables.

Reply 5: Thank you very much for your suggestion. We have already modified it in the article.

Changes in the text: Line69,29