

Peer Review File

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Reviewer A

Methodology

Comment Methodology-a: In the methodology, the authors should present precise criteria for including patients in the analysis.

Reply Methodology-a: As outlined in the introduction, this study aims to report on the recovery outcomes of patients with vocal cord palsy following oesophagectomy for oesophageal cancer, as well as the clinical significance of the management strategies employed during their recovery process.

Changes in the text Methodology-a: We revised the sentences from lines 66 to 74 on page 4 to clarify our intended message.

Comment Methodology-b: The authors should refer to the conducted preoperative diagnostics. Were patients subjected to classical bronchoscopy with an assessment of vocal cord function, or was bronchoscopy and ultrasonographic oesophagoscopy performed in the diagnostic process?

Reply Methodology-b: "We utilize diagnostic tools, including oesophageal endoscopy, oesophageal ultrasound, and CT scans, to determine the stage of oesophageal cancer. However, bronchoscopy is not conducted preoperatively to assess for vocal cord paralysis. The patient cohort for this study comprised individuals who exhibited new symptoms indicative of vocal cord paralysis following surgery.

Changes in the text Methodology-b: Due to overlap with Comment A, the corrections have been incorporated into lines 78-80 on page 4.

Comment Methodology-c: Although the table presents the locations of the tumor infiltration with statistical analysis, it is difficult to infer its impact on the occurrence of complications. I suggest presenting an analysis of the location of the tumor infiltration and its impact on the occurrence of complications (location of the tumor infiltration above and below the tracheal bifurcation).

Reply Methodology-c: We acknowledge the reviewer's remark regarding the significant correlation between tumor location relative to the tracheal bifurcation and recurrent laryngeal nerve paralysis. Due to the close anatomical proximity of RLN to the oesophagus at the cervical level, the incidence of RLNP is notably high in cases of cervical anastomosis. However, the scope of this study was not to investigate the incidence of recurrent laryngeal nerve injury and vocal cord palsy, but rather to focus on patients who had already developed vocal cord palsy. As such, we recognize this aspect as a limitation of our current study and intend to address it in future research.

Changes in the text Methodology-c: The issue highlighted by the reviewer is addressed in the Discussion section (line 247-250 on page 10, line 300-302 on page 12).

Comment Methodology-d: Similar reference should be made to the location of the anastomosis. It would be beneficial to address its impact on the occurrence of complications. Reference in the results and discussion.

Reply Methodology-d: Similar answer to comment-c. We added the contents and also references in the discussion section.

Changes in the text Methodology-d: line 247-250 on page 10.

Comment Methodology-e: The technique of the performed esophageal resection, lymphadenectomy, and the tools used should be accurately presented.

Reply Methodology-e: The surgical procedure and the fields of lymphadenectomy (2FL or 3FL) are detailed in the 'Surgical procedure' section of the manuscript. Regarding the use of devices, we believe it is not necessary to specify them individually, as the energy devices employed (harmonic scalpel, LigaSure, Thunderbeat) are standard in contemporary thoracic surgery.

Changes in the text Methodology-e: Line 98-107 on page 5.

Comment Methodology-f: A small group of patients underwent preoperative chemoradiotherapy. Despite this, I suggest providing the location of the tumor infiltration and potential statistical analysis for the occurrence of the analyzed complication. Did complications, especially damage to the recurrent laryngeal nerve, statistically dominate more frequently in the group of patients after chemoradiotherapy?

Reply Methodology-f: As the reviewer pointed out, we agree that neoadjuvant treatment may indeed be related to the incidence of recurrent laryngeal nerve injuries. However, as stated in our response to the previous comment, the focus of this study is on the recovery of patients who have already developed vocal cord palsy, rather than on the incidence of such conditions. Therefore, this aspect falls outside the scope of our current research and is acknowledged as a limitation.

Change in the text Methodology-f: None.

Comment Methodology-g: I suggest describing the diagnostic techniques for recognizing vocal cord damage.

Reply Methodology-g: As detailed in the 'Assessment of Vocal Cord Palsy' section, all patients suspected of having vocal cord palsy were referred to an otolaryngologist for laryngoscopy.

Changes in the text Methodology-g: Line 300-302 on page 9.

Results

Comment Result-a: The statement requires a detailed description of the number/percent

Reply Result-a: We have incorporated the reviewer's suggestions and revised the manuscript to the recommended format.

Changes in the text Result-a: Line 154-157 on page 7, Line 182-183 on page 8.

Comment Result-b: Were patients with squamous cell carcinoma subjected to chemotherapy or chemo-radiotherapy?

Reply Result-b: The effectiveness of adjuvant chemotherapy for esophageal squamous cell carcinoma is still debated. In our hospital, the decision to administer adjuvant therapy post-

surgery is made by a multidisciplinary team of oncologists, considering both the tumor characteristics and the patient's overall condition. In this study population, among the 189 patients included in this study, 41 (21.7%) underwent adjuvant treatment.

Changes in the text Result-b: None.

Discussion

Comment Discussion: I would suggest in the discussion to primarily address the risk factors listed above

Reply Discussion: In this paper, we examine the factors related to recovery in patients suffering from vocal cord palsy following oesophagectomy. Through multivariable analysis, the T stage emerged as the sole significant factor influencing recovery. In our discussion, we explore the impact of the T stage on recovery outcomes and further share our institution's strategies for patient management. Consequently, we believe the comments from the reviewer have been adequately addressed.

Changes in the Text: Line 247-250 on page 7.

Reviewer B

The authors investigated the management and outcomes of patients who experienced recurrent laryngeal palsy after oesophagectomy for oesophageal cancer. They demonstrated their strategy for patients with RLNP and concluded that the appropriate management reduced postoperative complications. Although this manuscript may provide helpful information for readers, there are several problems in this manuscript, as follows.

Comment 1: The results shown in the tables compare unilateral and bilateral RLNP. However, no data suggested how appropriate their strategy was.

Reply 1: In this study, we initially compared the baseline characteristics and postoperative outcomes between patient groups with unilateral and bilateral RLNP. In the postoperative outcome, bilateral RLNP naturally had high instability in respiratory function and a high possibility of aspiration, so the rate of tracheostomy and feeding jejunostomy was high, and the time for HA injection and oral feeding was long. Despite these differences, our analysis revealed no statistically significant disparity in the recovery duration between the unilateral and bilateral RLNP groups. Furthermore, multivariate analysis indicated that the direction of RLNP, its bilaterality, and recovery outcomes did not possess statistical significance.

Should there be suggestions for additional comparisons or analyses, we welcome your comments and are open to considering them to enrich our study further.

Changes in the Text: None.

Comment 2: The authors have not shown the number of oesophagectomies in this study period; therefore, the incidence of RLNP remains unclear.

Reply 2: During the study period, a total of 987 individuals underwent oesophagectomy for oesophageal cancer. Among these, 189 individuals, representing approximately 20%, developed RLNP. Details of this are provided in the Methods section.

The primary aim of this study was not to ascertain the incidence of RLNP but to identify factors associated with the recovery of patients who have already been diagnosed with RLNP. Furthermore, we aimed to present the management strategies employed by our institution for such patients.

Changes in the Text: None. (The reviewer's questions are described on lines 83-85 on page 4.)

Comment 3: Hopefully, complications and outcomes should be compared between patients who suffered RLNP and those without.

Reply 3: Feedback from several reviewers highlighted that the methodology section of our paper was not clear enough. To address this, we have revised the introduction to more clearly explain the rationale behind initiating our research on this topic. Previous research has extensively documented the consequences of RLNP, including prolonged hospital stays, increased pulmonary complications, and delayed onset of oral feeding. These impacts are well-established in the literature, a fact we now underscore with additional references in the introduction to provide context. Given this background, our study shifts the focus from the well-trodden path of examining the occurrence of RLNP to exploring the factors and clinical trajectory associated with RLNP recovery. This pivot is crucial for advancing our understanding of RLNP beyond its initial implications, aiming to uncover insights that could inform more effective management and rehabilitation strategies for affected patients.

Changes in the Text: line 66-74 on Page 4

4. The median HI time of 10 days seems too early because most RLNPs after oesophagectomy recover within 3 to 6 months.

Reply 4: We interpret the "HI time of 10 days" mentioned by the reviewer as referring to the HA injection time discussed in this study. While it may be perceived as brief, it represents a pivotal aspect of our institution's treatment strategy that we wish to highlight. As demonstrated in Table 3, the timing of the HA injection does not significantly influence recovery outcomes. Thus, we argue that irrespective of whether RLNP is temporary or permanent, promptly initiating intervention—coupled with aggressive rehabilitation to mitigate swallowing disturbances and minimize the risk of aspiration—is crucial for enhancing recovery. We respectfully request a reconsideration of the significance of our research. We aim to convey the effectiveness of this approach through our study.

Changes in text: None.

Reviewer C

This comprehensive article provides valuable insights from a thoracic surgeon perspective, including a detailed study on the clinical course of patients with recurrent laryngeal nerve paralysis (RLNP). I have some comments as follows.

Comment 1: Most RLNP were known to recover postoperatively and were not novel.

Reply 1: At the outset of our research, we were guided by previous studies and our clinical experiences which have established that RLNP typically undergoes natural recovery. However, the core objective of our paper was to elucidate the specific role that thoracic surgeons should play in supporting patients through this natural recovery process. Our investigation was driven

by the belief that merely waiting for spontaneous recovery from RLNP is insufficient. We argue that it is crucial to facilitate a return to normalcy—or as close to it as possible—for patients before the natural resolution of RLNP. This can be achieved through proactive intervention and targeted rehabilitation strategies. By emphasizing this approach, we aim to underscore the importance of a more dynamic and supportive role for thoracic surgeons in the management of RLNP, beyond passive observation. Our research seeks to highlight and advocate for the implementation of measures that can significantly enhance the quality of life for patients during the recovery phase, paving the way for a more holistic and patient-centered approach to RLNP care.

Changes in the Text 1: None

Comment 2: The authors concluded that hyaluronic acid injections and rehabilitation were important, but did not present data from statistical analysis.

Reply 2: We believe you've highlighted a crucial point. Thank you for the insightful comment. We believe it is crucial to emphasize a distinctive approach practiced at our hospital—swift administration of HA injection upon symptom onset. The one of the aims of our study was to demonstrate that early HA injection, irrespective of permanent damage to the RLN, does not impede the recovery from RLNP and yields positive outcomes.

However, our study encountered a limitation in directly comparing the recovery outcomes between patients who received immediate HA injections and those who did not. Recognizing this constraint, we intend to delve deeper into this aspect in future research endeavors. Our goal is to conduct comprehensive studies or meta-analyses involving larger patient cohorts to robustly assess the effects on RLNP recovery.

Changes in the Text: Line 298 to 300 in Page 12

Comment 3: Consideration of the relationship between factors in the development of RLNP (e.g., traction and thermal injury) and recovery may be required.

Reply 3: Thank you for highlighting critical points with such precision. The primary cause of RLNP is identified as either traction injury or thermal injury from energy devices, which are almost inevitable during surgical procedures. Despite recognizing these as risk factors for RLNP, we have yet to develop a method for quantitatively assessing which specific factors contribute and to what extent they affect the surgical process. Consequently, we attempted to assess indirect indicators such as robot-assisted oesophagectomy, central neck dissection, positive recurrent laryngeal nerve lymph node involvement, and the number of dissected lymph nodes. However, our study found no significant correlation between these factors and RLNP recovery. Looking forward, it would be beneficial to conduct a study comparing the prognosis based on the type of injury incurred during surgery, utilizing intraoperative RLN monitoring.

Changes in the Text 3: Line 296-297 on page 12

Reviewer D

This is a retrospective study to report the clinical course of patients with recurrent laryngeal nerve paralysis (RLNP) after esophagectomy. There are some points to revise, although I think it is an interesting study with early intervention to prevent mortality.

Comment 1: There is a certain probability of patients with asymptomatic RLNP after oesophageal surgery. Among them, there must be patients with pneumonia due to silent aspiration. Why don't you request the check of all patients by otolaryngologist?

Reply 1: Screening all patients for silent Recurrent Laryngeal Nerve Palsy (RLNP) would undoubtedly aid in diagnosis, yet it is anticipated to impose a significant burden on both our team, the otolaryngologists, and the patients. However, at our institution, we strive to screen as many patients with suspected RLNP as possible. To this end, patients exhibiting potential signs of pneumonia without any other identifiable cause, as determined through daily chest X-rays, are also considered for laryngoscopy. We believe this approach significantly reduces the likelihood of overlooking affected patients. Recognizing the necessity of this description, it has been incorporated into the 'Assessment of Vocal Cord Palsy' section.

Changes in the Text: line 116-120 on page 6.

Comment 2: Is there any relationship between paralysis recovery and 2 or 3 field lymph node dissection?

Reply 2: In our institution, three-field lymphadenectomy was conducted, targeting the 2FL stations and cervical lymph nodes. Cervical node dissection was carried out by an otolaryngologist. Consequently, all patients who underwent 2FL also received cervical node dissection (CND). Recurrent laryngeal nerve palsy tended to be increased in the 2FL group compared to the 3FD group. A reference to that part has been added. In this study, the analysis revealed that the difference in recovery between patient groups who underwent CND was not statistically significant.

Changes in the Text: line 236 on page 10 (reference added)

Comment 3: There is no description about the relationship between duration of the operation and paralysis recovery. Please mention it.

Reply 3: We believe that the extended surgical duration in the thoracic phase, as discussed, is a contributing factor to recovery outcomes. This might be particularly relevant to the traction and thermal injuries highlighted by other reviewers. While we recognize its importance, the retrospective nature of our study limited our ability to analyze this aspect due to the absence of separately recorded surgical times for the thoracic phase. We intend to address this limitation and ensure a more thorough examination in future research.

Changes in the Text 3: Line 296-297 on page 12.

Comment 4: You emphasize the management of RLNP. You should describe the method of intracordal HA injection in detail. If possible, please add figures about it.

Reply 4: The HA injection laryngoplasty technique employed in our institution aligns with the method most commonly utilized in current studies. The HA injection is administered using a trans-cervical approach via a cricothyroid membrane puncture, under local anesthesia. This procedure is performed with the aid of flexible laryngoscopy, on patients in a sitting position. In concordance with the reviewer's suggestion, the relevant content has been incorporated into the manuscript. However, as HA injection laryngoplasty itself is a well-known practice and not the central subject of this paper, we have included a reference that provides detailed information on this topic for those interested in further exploration.

Changes in the Text 4: Line 131-133 in page 6.

Comment 5: There are some written mistakes. For example, Line 138 (... chemotherapy to 73 38.6%) patientrts.) Line 161(... followed by aspiration (20.1. During ...). Please make spell check strictly.

Reply 5: I extend my sincere apologies to the reviewers for the oversight in this part of the manuscript, which was likely introduced during the internal revision process. A correction has been made and applied to address this issue."

Changes in the Text 5: followed by aspiration (n=38, 20.1%). / chemotherapy to 73 (38.6%) patients

Reviewer E

While I appreciate your effort on Recurrent Laryngeal Nerve Paralysis following oesophagectomy, this manuscript is interesting for the esophageal surgeon. You have referred to 'Only the T stage affected nerve recovery'.

I have some questions.

Comment 1: In Methods, you wrote oesophagectomy was performed via open thoracostomy, video-assisted thoracoscopic oesophagectomy (VE), or robot-assisted oesophagectomy (RAE). You should write the indications of these differences.

Reply 1: The surgical approaches, whether open, VATS (Video-Assisted Thoracoscopic Surgery), or RAT (Robot-Assisted Thoracotomy), were selected based on an optimal method that considered various complex factors, including the patient's stage of disease, underlying conditions, the surgeon's preferences, and the patient's financial situation. Our study focused on the prognosis and clinical course following recurrent laryngeal nerve injury, without addressing the incidence of such injuries. Given the retrospective nature and specific objectives of this study, I believe it is unnecessary to detail the indications for each surgical approach. I kindly ask you to reconsider this aspect once again.

Changes in the text: None.

Comment 2: Although it is a similar question, you wrote More than half of the study group (58.7%) underwent cervical anastomosis, while 41.3% of the patients underwent intrathoracic anastomosis. What are the differences in this indication? If you choose the intrathoracic anastomosis, number of the RLN LN retrieved will decrease?

Reply 2: The selection between the two procedures is influenced by the tumor's location and the extent of lymph node involvement. Thoracic anastomosis is typically favored for tumors situated in the middle to lower regions of the oesophagus, whereas cervical anastomosis is commonly employed for tumors in the upper oesophagus. At our institution, the standard surgical approach for early-stage ESCC consists of transthoracic oesophagectomy, gastric pull-up via a posterior mediastinal route, and standard 2FL dissection. We aim to comprehensively perform superior mediastinal lymphadenectomy, including dissection at bilateral RLN lymph node stations, for all eligible patients undergoing oesophagectomy, whenever feasible.

Changes in the Text: None.

Comment 3: You found that the mean number of LN dissected was 37 (36.6 ± 14.3), and statistically, more LN dissections were performed in the bilateral RLNP group than in the unilateral RLNP group ($p=0.02$). You should describe not only the total number of LN but also the thoracic total number of LN. Although there is no significant difference in operation, stage, location, and pathological result, why RLNP group were dissected more?

Reply 3: We believe there may be a misunderstanding regarding the causal relationship between lymphadenectomy and recurrent laryngeal nerve palsy (RLNP). Our intention is not to suggest that performing more lymphadenectomy results in bilateral RLNP among patients. Instead, our retrospective analysis indicates that a higher incidence of bilateral RLNP was observed among patients who underwent more extensive lymphadenectomy. We aim to clarify this distinction and highlight the directionality of the relationship as observed in our study findings.

Changes in the Text: None.

Comment 4: You wrote that pathologic T3 and T4 were poor prognostic factors for RLNP recovery. The advanced T stage is linked to LN metastasis and a neoadjuvant treatment target. Although such an advanced oesophageal cancer has sometimes RLN LN metastasis, you only suggested the number of clinical T stages. Moreover, you did not have cT4 cases in this study. But you have pT4 cases. How many cases?

Reply 4: First, a total of 3 patients were confirmed to have T4 at the pathological T stage. The meaning might not have been clearly conveyed in Table 1's basic characteristics due to unclear expressions. The previous term "RLN metastasis" referred to "RLN lymph node metastasis". However, multivariate analysis to determine factors influencing recovery showed that the presence or absence of RLN metastasis did not have a statistically significant impact. In addition to this, tables that could potentially cause confusion have been corrected.

Changes in the Text: Tables 1.

Comment 5: Although it is a similar previous suggestion, you don't have clinical T4 cases. But you have more than 10% cases of R1/R2 cases. This means such a highly advanced case is a cT4 case and it is not an indication of surgery. It depends on the accuracy of clinical diagnosis and needed neoadjuvant radiotherapy.

Reply 5: To clarify the data, R1 and R2 were presented separately. R2 comprised a total of two individuals, with one case each of unilateral and bilateral RLNP. In our institution, the pre-operative staging system included endoscopic ultrasound (EUS), chest computed tomography (CT), abdominal CT, pelvic CT, and positron emission tomography (PET) scanning as per NCCN guidelines. If a lymph node metastasis was suspected by imaging modalities, EUS or endobronchial ultrasound (EBUS)-guided fine needle aspiration followed to confirm findings. After staging, patients who had locally advanced disease ($\geq T2$ or $\geq N1$) received neoadjuvant CRT, except when the patient was over 75 years of age or in poor physical condition, according to the oncologist's judgment from a multidisciplinary oncologic clinic.

Changes in the Text: Table 1, line 89-91 in page 5.

Comment 6: You have a total of 5.3% of pulmonary complications. But you have 20% of aspiration patients. What is the diagnosis tool of your hospital for pneumonia? And also you had better use the Clavien-Dindo classification when you resulted in complications.

Reply 6: The aspiration sign was defined as the abnormal occurrence of cough reflex and the failure of normal swallowing during the initial oral feeding test phase following oesophagectomy. Patients with sufficient coughing strength may prevent the progression to pneumonia, even if aspiration signs are present. Pneumonia was characterized by high fever, purulent sputum, leukocytosis in blood tests, and the presence of infiltrates on chest X-rays. We concur with the reviewer's recommendation regarding the significance of the Clavien-Dindo classification. However, given the retrospective nature of our study, we encountered practical challenges in gathering the pertinent data. We intend to actively incorporate this consideration into our future research endeavors.

Changes in the Text: line 116-118 on page 6.

Minor suggestion

Also, I do see the need for some correction, and I hope you can share my arguments below.

Comment 1: It is referred in the Result(Line138) 'We administered neoadjuvant chemotherapy to 73 38.%)'. It looks you have forgotten to add a bracket. Please add them.

Reply 1: Despite multiple checks before submission, typos likely occurred during the internal revision process. Thank you very much for your meticulous review of the manuscript.

Changes in the text: 73 (38.6%)

Comment 2: In the operative details robot-assisted oesophagectomy was performed(Line146). How was the robot-assisted oesophagectomy performed, right thoracotomy or transhiatal? In Methods(67-68), it is not referred about transhiatal. Please add them.

Reply 2: The right thoracic approach was utilized in almost all cases, encompassing both open and video-assisted surgery, as well as robot-assisted surgery. Additionally, information on the technique of transhiatal oesophagectomy has been included.

Change in the text: line 99-106 on page 5.

Comment 3: It is referred in the Results(Line161) 'aspiration(20.1.'. It looks you have forgotten to add a bracket and a %. Please add them.

Reply 3: Despite multiple checks before submission, typos likely occurred during the internal revision process. Thank you very much for your meticulous review of the manuscript.

Change in the text: (n=38, 20.1%)