Peer review file

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Reviewer A

Comment 1: Vocal Cord Injury/Palsy is graded according to the Esophagectomy Complications Consensus Group.Type I's are most common and, generally speaking, no major concern. Type 3's, however, are serious and if they were to occur 8/30 times would suggest this technique is not a suitable alternative to TLE. Could the authors indicate what level of injury was observed and how this was assessed?

Reply 1: We sincerely appreciate for your thoughtful comments and critical suggestions. The patient's vocal cord injury/palsy was assessed on the first day after the operation. A total of 13 patients had hoarseness: 8 in the MATHE group and 5 in the TLE group. They had changes in the sound of their voice, and they demonstrated the inability to raise their voice in volume. However, they had no difficulties swallowing or breathing, and they did not experience frequent choking while eating or drinking 2 weeks after surgery. According to the Clavien-Dindo (CD) and the Esophagectomy Complications Consensus Group (ECCG) classifications, all 13 patients had type I, vocal cord injury/palsy, which indicates a transient injury requiring no therapy.[1]

Changes in the text: We have modified our text as advised (we added text in red font, see in Page 13, line 263-270). At the same time, we add a reference: 10. Low DE, Alderson D, Cecconello I, et al. International Consensus on Standardization of Data Collection for Complications Associated With Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg 2015;262:286-94.

Comment 2: The follow up is not specified (recruitment is), and it would be good to include this and comment on early oncological outcomes.

Reply 2: Follow-up by telephone and outpatient reexamination revealed a median follow-up time of 11.2 months (ranging from 2 to 24 months). During the routine examination after the operation, 1 patient had liver metastasis in the TLE group. Furthermore, 1 patient had lung metastasis in the MATHE group.

Changes in the text: We have modified our text as advised (we added text in red font,

see in Page 13-14, line 271-274). And we added some data. (see Page 14, red font in TABLE 2)

Comment 3: The paper would benefit from input from a native English speaker as there are quite a few syntax errors/unusual expressions.

Reply 3: The revised article has been submitted to AJE (English Editing & Author Services for Research Publication) for polishing and revision by native English speakers. We enclose the Editing Certificate.

Reviewer B

Hereby I would like to give my comments to the manuscript entitled:
"Mediastinoscopy-assisted transhiatal esophagectomy versus thoraco-laparoscopic esophagectomy for esophageal cancer: A single-center initial experience."by the authors Liu et al.
In this manuscript the authors retrospectively compare a new approach for esophagectomy via mediastonoscopy (MATHE) with a conventional technique. It is interesting to read about this new approach, however, I also have some concerns.

- The MATHE approach seems to be developed to perform a more radical lymphadenectomy, while potentially reducing pulmonary complications. However, the authors show no difference in lymph node yield, no differences in pulmonary complications and even more hoarseness indicative of RLN palsy in the MATHE group. How are these results explained? Is there a learning curve? Based on these results, I think the conclusions need to be adapted.

Comment 1: The MATHE approach seems to be developed to perform a more radical lymphadenectomy, while potentially reducing pulmonary complications. However, the authors show no difference in lymph node yield, no differences in pulmonary complications and even more hoarseness indicative of RLN palsy in the MATHE group. How are these results explained? Is there a learning curve? Based on these results, I think the conclusions need to be adapted.

Reply 1: In the MATHE approach, we insert the operating devices along the

esophagus from the cervical and hiatal sides, which allows for smooth dissection of the esophagus and regional lymph nodes from the surrounding organs, this may leads to a more radical lymphadenectomy. However, there is still major difficulty with lymphadenectomy in terms of the deep mediastinal space around the aortic arch and tracheal bifurcation due to the narrow operation space and limited vision. Therefore, there was no significant difference between MATHE and TLE in terms of the number of lymph nodes dissected in our study.

In the study, MATHE did not show a lower incidence of postoperative pulmonary complications. Maybe it's because we have carried out TLE procedure for many years, and it had a low incidence of postoperative complications. It needs to be proved by further study.

A similar result in the incidence of vocal cord palsy was reported between patients who underwent transthoracic esophagectomy with upper mediastinal dissection via transthoracic and bilateral transcervical approaches (32.7% vs. 35.7%). These fndings suggest that the risk of vocal cord palsy may be equivalent between transthoracic and transcervical approaches if lymphadenectomy along the bilateral RLNs is performed.[2]

We reviewed the 30 patients who underwent MATHE, and the incidence of hoarseness was 33.3%(5/15) for the first 15 patients, and 20%(3/15) for the later 15 patients. This may indicate that improvements in surgical skills can reduce the incidence of vocal cord palsy, but there is a possibility of bias due to the small sample size of patients undergoing this surgery, and it is still necessary to explore whether there is a learning curve.

Changes in the text: We have modified our text as advised (we added text in red font, see in Page 15, line 297-302 and Page 16-17, line 324-328).

Comment 2: What is the experience of the operating surgeon (s) with MATHE before start of this study? This needs to be documented as well as the way it has been introduced in this hospital. Was there informed consent obtained from the patients?

Reply 2: The surgeons had rich experience in mediastinal lymph node biopsy and resection with traditional mediastinoscopy. After applying the MATHE as a new technology and new project in our hospital, a total of 8 MATHE procedures were performed in 2017. The patients included in this study were all recruited after 2018.

All patients who received the procedure signed informed consent forms.
Changes in the text: We have modified our text as advised (we added text in red font, see in Page 5, line 98-102).

Comment 3: The rationale to perform MATHE is not clearly put forward.

Reply 3: The mediastinum, the space behind the sternum in the middle of the chest, is situated between the 2 lungs. It contains the heart and its great vessels and the trachea, esophagus, thymus gland and lymph nodes. This area can be examined with a tool called a mediastinoscope. The rationale of MATHE is to establish artificial pneumomediastinum and explore the mediastinal structures with a video-assisted procedure, through which esophageal dissociation and lymphadenectomy can be completed.
Changes in the text: We have modified our text as advised (we added text in red font, see in Page 8, line 142-148).

Comment 4: Did the authors objective recurrent laryngeal nerve palsy in patients with hoarseness? In the methods section is mentioned that hoarseness was assessed on the first day postoperatively, however the method of assessment is lacking. How do the authors explain this difference between groups?

Reply 4: Yes, we objective to compare the recurrent laryngeal nerve palsy in patients with hoarseness. The patient's vocal cord injury/palsy was assessed on the first day after the operation. A total of 13 patients had hoarseness: 8 in the MATHE group and 5 in the TLE group. They had changes in the sound of their voice, and they demonstrated the inability to raise their voice in volume. However, they had no difficulties swallowing or breathing, and they did not experience frequent choking while eating or drinking 2 weeks after surgery. According to the Clavien-Dindo (CD) and the Esophagectomy Complications Consensus Group (ECCG) classifications, all 13 patients had type I, vocal cord injury/palsy, which indicates a transient injury requiring no therapy.

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size of patients undergoing this surgery, and it is still necessary to explore whether there is a learning curve. While TLE is a proven technology in our department which had perform for many years. In this study, we observed that the incidence of hoarseness in TLE group is lower than that in MATHE group, whether is because MATHE is still in the learning curve or the technology of MAHTE itself has a higher incidence of hoarseness, we can't easily come to a conclusion.

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Comment 5: Table 1 mentions absolute numbers of patients per stage, I would suggest using %

Reply 5: We have modified our data as advised.

Changes in the text: We have modified our data as advised. (see Page 6, red font in TABLE 1)".

Comment 6: In the methods section is mentioned that patients received "….anti-inflammatory, hemostatic, phlegm-resolving treatment, nutritional support and pain management." This needs some further explanation.

Reply 6: All patients received second-generation cephalosporins for prophylactic anti-infective treatment, conventional analgesic treatment with weak opioid or nonsteroidal analgesics, and the best nutritional support treatment (through intravenous or enteral nutrition) untill the patient recovered to a semifluid diet and until routine treatment with atomization and expectoration was adiministered after the operation. If there was substantial blood drainage after the operation, hemostatic drugs were given properly.

Changes in the text: We have modified our text as advised (we added text in red font, see in Page 11-12, line 227-233).

Comment 7: In the introduction it must be made more clear that the McKeown

approach is needed for higher esophageal tumours. There are also other techniques available.

Reply 7: The anatomical features of the esophagus fundamentally determine the diversity of surgical approaches and methods. The esophagus is located in the posterior mediastinum and crosses the neck, chest and abdomen longitudinally. The left thoracic, right thoracic and mediastinal approaches are the three main surgical approaches for esophageal cancer. The classic left thoracic approach includes conventional left thoracotomy esophagectomy and a transthoracic combined left cervical incision. The right thoracic approach includes two incisions (right posterolateral thoracic incision + mid-upper abdominal incision) and three incisions (left neck incision + right posterolateral thoracic incision + mid-upper abdominal incision) as well as thoracoscopic and laparoscopic minimally invasive two- or three-incision esophagectomy. There are several techniques available for esophageal cancer. When esophageal tumours have a high location, the McKeown approach is needed.Thank you for your comments. We have added other technologies to the introduction in detail.
Changes in the text: We have modified our text as advised (we added text in red font, see in Page 3-4, line 56-68).