

Peer Review File

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Reviewer A:

Thank you for the opportunity to review this manuscript. The manuscript submitted by Xiao-Kun Li et al. reports that the ratio of the gastric conduit length to the thorax length can reflect the tension in the anastomosis, which can reduce AL by adjusting the length of the gastric conduit. Before this manuscript can be considered suitable for publication in *Annals of Translational Medicine*, major and minor concerns listed as below should be answered.

Answer: Thank you so much for your time and efforts to this article. We have revised the manuscript according to your helpful suggestions.

Major concerns

Comment 1: Measurement and definition of the thoracic length in the manuscript does not seem suitable to adapt for the actual length of the posterior mediastinum route. Different from a retrosternal route, anatomical length of posterior mediastinum route, in some cases, may differ to the length of measurement modality in the manuscript by spinal curvature.

Answer 1: Originally, we wanted to measure the length of the native esophagus starting from the surface projection of the cardia to the cervical anastomotic site. However, difficulties existed: locating the surface projection of the cardia is difficult; as for the cervical anastomotic site, the position of the incision in the neck is not certain before anastomosis. Therefore, an alternative highly standardized method to measure the length featuring two definite and easy-to-locate endpoints should be employed. First, we took into consideration the length from the spinous process of the 1st thoracic vertebra to the spinous process of the 12th thoracic vertebra; however, this length could be easily affected by scoliosis and kyphosis. Then, the length from the xiphoid to the sternal notch was considered. However, this measure was easily affected by sex and BMI (body mass index) and could not precisely represent the length of the native esophageal bed in the posterior mediastinum. Finally, we chose the horizontal length of the thorax, which was defined as the distance between the start at the xiphoid and the

end of the sternal notch; this measure correlates to the length of the native esophageal bed more precisely. The revision is in red.

Change 1: Originally, we wanted to measure the length of the native esophagus starting from the surface projection of the cardia to the cervical anastomotic site. However, difficulties existed: locating the surface projection of the cardia is difficult; as for the cervical anastomotic site, the position of the incision in the neck is not certain before anastomosis. Therefore, an alternative highly standardized method to measure the length featuring two definite and easy-to-locate endpoints should be employed. First, we took into consideration the length from the spinous process of the 1st thoracic vertebra to the spinous process of the 12th thoracic vertebra; however, this length could be easily affected by scoliosis and kyphosis. Then, the length from the xiphoid to the sternal notch was considered. However, this measure was easily affected by sex and BMI (body mass index) and could not precisely represent the length of the native esophageal bed in the posterior mediastinum. Finally, we chose the horizontal length of the thorax, which was defined as the distance between the start at the xiphoid and the end of the sternal notch; this measure correlates to the length of the native esophageal bed more precisely.

Comment 2: Authors concluded in the manuscript that tension of the gastric tube at anastomosis influenced AL. Though authors have mentioned in the discussion that anastomotic healing is affected by several factors including blood supply, why did authors not take vascularization of the gastric conduit into consideration as the analysis factor of AL. Further, anastomotic tension is not only caused by the gastric tube length but also by a tension while passing narrow thoracic inlet. The analysis without those factors is vulnerable and unreliable.

Answer 2: Blood supply is a major factor influencing the rate of anastomotic leakage after esophagectomy. However, even though the vascularization of gastric conduit was performed after the construction of gastric conduit, there was no unified standard to detect the condition of blood supply, which relies on surgeons' clinical experience, resulting in it difficult to take vascularization of gastric conduit into logistic regression. Anastomotic tension is also influenced by a tension while the gastric tube passing through the narrow thoracic inlet. Nevertheless, the diameters of thoracic inlet in different patients were relatively equal and the lengths of gastric conduit we pulled out at the anastomotic site were similar in each esophagectomy before anastomosis.

Therefore, the diameter of thoracic inlet was not taken into consideration as a factor influencing anastomotic tension. The revision is in red.

Change 2: Blood supply is a major factor influencing the rate of anastomotic leakage after esophagectomy. However, even though the vascularization of gastric conduit was performed after the construction of gastric conduit, there was no unified standard to detect the condition of blood supply, which relies on surgeons' clinical experience, resulting in it difficult to take vascularization of gastric conduit into logistic regression. Anastomotic tension is also influenced by a tension while the gastric tube passing through the narrow thoracic inlet. Nevertheless, the diameters of thoracic inlet in different patients were relatively equal and the lengths of gastric conduit we pulled out at the anastomotic site were similar in each esophagectomy before anastomosis. Therefore, the diameter of thoracic inlet was not taken into consideration as a factor influencing anastomotic tension.

Comment 3: Why did authors mention that RATS had lower AL compared with open operations. According to table 2, open operation had a lower incidence rate of AL at 6.7% (9/137) than that of RATS at 12.8% (5/39).

Answer 3: Sorry for our negligence in statistical procedure. The correct coefficient and standard error were listed in the revised version. The revision is in red.

Change 3: Compared with operation type 1 (open operation), operation type 2 (VATS) showed a higher AL incidence.

The results showed that open operations yielded a lower AL incidence compared with VATs. The results may be caused by the collection bias since the number of patients included in this study was limited. Therefore, we propose further studies to explore the effect of these three surgical methods on postoperative complications.

Comment 4: What is a meaning for authors to describe detailed statistical procedure using a quite amount of words.

Answer 4: Thank you for your suggestions. The statistical procedure in this study is an advanced method to determine a cut-off value in this kind of data. Only a few clinical studies adopt this method. However, its reliability and accuracy have been identified by many statistical experts in different studies. Therefore, in this study, we describe the detailed statistical procedure to make it easy for clinicians to use this method in the

future studies. There are some reduplicative contents in the statistical section. We have deleted them in the revision. The revision is in red.

Change 4: We conducted a dichotomized analysis comprising an exploratory analysis (graphical diagnostic plots) and an exact search (the minimum p-value approach) to determine the exact cut-off point. A scatter plot and a grouped data plot were drawn in the former stage to help uncover the underlying relationship between the ratio and AL as well as preliminarily to frame an interval for the potential cut-off point.

Minor concerns

Comment 1: I think P9,/line 289 is not table 2 but table 4

Answer 1: Thank you for your kind notification.

Change 1: The Figure 2 was changed into Figure 4 in the revised version.

Comment 2: Description of open surgical procedure in P4/line133 is not clear. Is this really left thoracotomy instead of right?

Answer 2: Thank you for your suggestion. The open operations in our institution were all left thoracotomy since is easy to expose the stomach through an incision in the left diaphragm. The revision is in red.

Change 2: The open operation started with a left thoracotomy, after which the esophagus was divided gently from the diaphragm to the apex of the chest. The stomach was explored through an incision in the left diaphragm. After a gastric conduit was created and pulled out into the thorax, the incision in the left diaphragm was sutured, then followed by the same VATS and RATS procedures.

Comment 3: Sentences in sections of statistical analysis at P5/line 164-167 and P5/line 167-171 are similar.

Answer 3: The sentences in sections of statistical analysis at P5/line 164-167 and P5/line 167-171 have revised. The revision is in red.

Change 3: We conducted a dichotomized analysis comprising an exploratory analysis (graphical diagnostic plots) and an exact search (the minimum p-value approach) to determine the exact cut-off point. A scatter plot and a grouped data plot were drawn in the former stage to help uncover the underlying relationship between the ratio and AL as well as preliminarily to frame an interval for the potential cut-off point.

Comment 4: What does the red color indicate (p3/line93-97, P11/line339-351, supplement table 2)

Answer 4: These are the revision according to the MDAT guidelines sent by editor.

Comment 5: Line spacing and font are not uniformed. (P2/line59-P3/line74, references, table 3)

Answer 5: Thank you for your notification. The line spacing and font have been uniformed.

Reviewer B:

I read the manuscript with interest as an oncological surgeon.

Authors retrospectively reviewed the clinical data of 273 patients who underwent esophagectomy. The incidence of AL was 12.5% (34/273). All the patients who underwent esophagectomy, which comprised open surgery, video-assisted thoracic surgery (VATS), and robot-assisted thoracic surgery (RATS).

The authors have planned the study very well, and the resulting leakage rate is quite low. One weak point of the work is its retrospective character, which does not diminish its value.

I think that the authors have answered appropriately reviewers' comments point-by-point and this article is now acceptable for Annals of Translational Medicine

Answer: Thank you so much for your time. We have revised the manuscript according to the suggestions given by other reviewers and editor. We believe that this article could be more suitable to be published in Annals of Translational Medicine after revision.