

Peer review file

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Reviewer A

Major comments:

Comment 1: Strongly consider adding secondary outcomes beyond overall survival. Otherwise there is really very little value to your hard work. (Does LTD decrease LOS, post op pneumonia or atrial fibrillation, etc).

Reply 1: Thank you for valuable suggestion. The fundamental purpose of this study was to compare the survival difference when we designed the study. From clinical experience, most of postoperative complications, such as pneumonia and atrial fibrillation, are temporary and can be cured before discharge. And in a previous study, no postoperative complications related to LTD were recorded (1). So at first postoperative complications weren't included in our study. However, just as you suggested, there is really very little value to our work, if we set overall survival as the only outcome. So we had included postoperative outcomes in the study but all of available data (such complications and LOS, et al) were not statistically different. We have included postoperative complications in our study.

Changes in the text: As shown in the RESULTS (see line 154-166), Table 1 and Table 2 ; (1) Guo Wei, Zhao Yun-Ping, Jiang Yao-Guang et al. Prevention of postoperative chylothorax with thoracic duct ligation during video-assisted thoracoscopic esophagectomy for cancer. Surg Endosc, 2012, 26: 1332-6.

Comment 2: We need to know how LTD vs non-ligation effected post op outcomes. This needs to be discussed and documented in a table.

Reply 2: Thank you for valuable suggestion. Just as the first question, we included postoperative complications in the study and described the incidence of each complications. Then Chi-square test was used to compare the difference between LG and NLG. And the results were discussed in the DISCUSSION. We described the incidence of each complications and compared the incidence between LG and NLG.

And the results were discussed in the DISCUSSION.

Changes in the text: as shown in the RESULTS (see line 154-166), DISCUSSION (see line 198-208), Table 1 and Table 2

Comment 3: It is obvious that English is a second language which is fine, but the grammar and syntax in several places that I marked need to be fixed. I recommend having a very good English scientific reader edit your text before re-submitting.

Reply 3: Thank you for valuable suggestion. All grammar and syntax errors in the manuscript have been corrected.

Changes in the text: Errors are revised and marked by Red.

Comment 4: The discussion is mostly discussing other papers and not the work of your own. I would recommend diving deeper into your results in the discussion to help the reader understand the significance of what you are trying to do.

Reply 4: Thank you for valuable suggestion. At first, the fundamental purpose of this study was to compare the survival difference, and differing from the Hou's study, the result showed that LTD had no negative impact on long-term survival in patients with esophageal cancer. So we pay more attention to investigate why LTD had no negative impact on long-term survival and neglected the discussion of our results themselves. So we modified this article and dived deeper into our results. We modified the discussion part and pay more attention to the work of our own.

Changes in the text: as shown in the DISCUSSION (see line 198-208; line 226-234).

Minor comments:

Multiple grammatical mistakes. Obvious that English is a second language.

-Line 33 – do not capitalize “The”

Reply: We modified the article and deleted this part.

-Conclusion that thoracic duct ligation has no prognostic value is actually only based on survival. Perhaps there are other factors that could be looked at (LOS, leak, etc.)

Reply: Thank you for valuable suggestion. Just as the first question in major comments, we finally included postoperative complications in the study and compare the incidence between LG and NLG. We described the incidence of major postoperative complications and compared the incidence between LG and NLG.

Changes in the text: as shown in the RESULTS (see line 154-166), Table 1 and Table 2

-Line 45: Prognosis should be capitalized

Reply: We have corrected this error in the manuscript. Thank you for your suggestion.

Changes in the text: as shown in Line 44

-Line 51/52 take out as reported.

Reply: We have taken it out.

Changes in the text: as shown in Line 69.

-I think it is important to differentiated esophagectomy for benign disease (e.g. end stage achalasia vs cancer) as this is a totally different patient cohort.

Reply: We have re-written it.

Changes in the text: as shown in line 69.

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-Line 62 needs a reference to Hou et al.

Reply: We have added the important information into the references.

Changes in the text: Reference 8 (line 301)

Reference

Hou X, Fu JH, Wang X, et al. Prophylactic thoracic duct ligation has unfavorable impact on overall survival in patients with resectable oesophageal cancer. Eur J Surg Oncol. 2014;40(12):1756-1762. doi:10.1016/j.ejso.2014.05.002

-Lines 63 – 69 needs to be re-written. I know what you are trying to say but needs to be clearer.

Reply: We have re-written 63-69.

Changes in the text: as shown in Line 76-80.

-What was the mode of esophagectomy (open, MIS, Robotic), two or three holes, etc?

Reply: Thank you for valuable suggestion. Minimally invasive surgery (MIS) could achieve survival rates and reduce perioperative complications, compared with open esophagectomy. We are sorry for this negligence in the study. Only open surgery and MIS have been included in our study. Total of 60 (16.30%) patients in the NLG received MIS, compared with 18.70% of patients in the LG ($p=0.449$). The ratio of different surgical approaches was shown in table 1 and table 2. We have added the mode of esophagectomy into the research.

Changes in the text: as shown in Line 148-150 and table 1.

-Line 76: I think what you mean to say is pathologically proven carcinoma.

Reply: We have re-written 76.

Changes in the text: as shown in Line 91.

-Line 78-79: complete medical record is enough.

Reply 1: We have re-written 78-79.

Changes in the text: as shown in Line 93.

-Line 82: you have not defined ESD or EMR.

Reply: We have defined ESD in Statistical analysis.

Changes in the text: as shown in Line 134-135.

-Line 85: cannot start a sentence with a number. Have to spell it out (Forty-six).

Reply: We have re-written 85.

Changes in the text: as shown in Line 97.

-Why did you eliminate neoadj patients? In the West, it is common for all patients to get neoadj for surgically resectable disease.

Reply: Thank you for valuable suggestion. Neoadjuvant chemoradiotherapy plus surgery is widely recognized as the best approach for local advanced ESCC nowadays. However, thoracic surgeons preferred the treatment model of surgery plus postoperative chemoradiotherapy nearly ten years ago. Thus, the patients adopting neoadjuvant chemoradiotherapy enrolled in this study is rare (only 9 patients). Given the small portion of these patients and potential confounders, we excluded these patients in the study. It's better to include these patients in PSM as you advised because PSM could eliminate the confounders between groups. We have included the patients with neoadjuvant chemoradiotherapy and run PSM.

Changes in the text: as shown in Line 134、148, Table 1 and Table 2.

-Can you please tell us how many surgeons were in the study and what their criteria were to ligate or not ligate the thoracic duct.

Reply: Thank you for your question. There are four surgical teams (each team contained chief surgeon, 1st assistant, 2nd assistant, et al) in this study. The thoracic duct was ligated when intraoperative chylous leakage occurred, or injury to the thoracic duct was highly suspected. We have described this problem in the methods part.

Changes in the text: as shown in Line 106-108.

-Line 105: This study has only one outcome datapoint (death); perhaps you should consider looking at additional secondary end points. This would be especially interesting since you had no significant result from your primary outcome.

Reply: Thank you for valuable suggestion. Just as the first question in major comments, we included postoperative complications in the study and compare incidence between LG and NLG. We described the incidence of each complications and compared the incidence between LG and NLG.

Changes in the text: as shown in the RESULTS (see line 154-166), Table 1 and Table 2.

-Line 123: it is “show” not showed.

Reply: We have re-written it.

Changes in the text: as shown in the line 142.

-Line 126: need to reword “more Sweet approach”.

Reply: We have re-written it.

Changes in the text: as shown in the line 148-150.

Line 132: “all of the baseline data were comparable...”

-Although not significant, why did LG have a better survival do you think? Better G1?

Reply: Thank you for your question. At first, the fundamental purpose of this study was to compare the survival difference, and the result was different from previous study, so we pay more attention to investigate why LTD had no negative impact on long-term survival and ignored our results themselves. We have discussed why did LG have a better survival in the discussion part. we have discussed why did LG have a better survival in the discussion part.

Changes in the text: as shown in the line 231-235.

-Line 144- 151 needs to be rewritten so that it reads clearer. I know what you mean but it is written awkwardly.

Reply: We have used the AME Editing Service for improving the grammar and syntax.

Changes in the text: as shown in the line 178-185.

-This seems to be a retrospective study, but you never come out and say this.

Reply: We have re-written it.

Changes in the text: as shown in the line 87, 256-257.

-Discussion

-Line 154- what previous study? Do you mean previous studies in general?

Comment: Thank you for your question. The previous study referred to Hou's study. It was our oversight not to add the reference.

Reply: we have re-written it.

Changes in the text: as shown in the line 189.

-154-55: were you expecting to LTD to have a negative impact?

Reply: Thank you for your question. We only want to emphasize the difference between

Changes in the text: None

-You do not report your chylothorax rate for this study or the impact it had on your cohort. This must be shown in a table and discussed.

Reply: Thank you for valuable suggestion. Just as the first question in major comments, we included chylothorax rate in the study and compare incidence between LG and NLG. Postoperative chylothorax occurred in 2 patients in the LG (0.83%) and 3 patients in the NLG (0.81%), with no significant difference ($p = 1.000$). Except for reoperation in 1 patient in the LG, the 4 other patients were treated with conservative approaches, and there were no hospital mortalities among these patients. We described the incidence of chylothorax and compared the incidence between LG and NLG.

Changes in the text: as shown in the RESULTS (line 156-159, 162-164), Table 1 and Table 2.

Reviewer B

Comment 1: (Patients and Methods, line 81) Why the authors exclude patients who underwent preoperative chemo or radiotherapy? Many of patients (especially SqCC) undergo preoperative chemoradiation before esophagectomy. Is there any specific reason for excluding these patients for evaluating the long-term effect of thoracic duct ligation? I would prefer including these patients and run PSM with this factor included.

Reply 1: Thank you for valuable suggestion. Neoadjuvant chemoradiotherapy plus surgery is widely recognized as the best approach for local advanced ESCC nowadays. However, thoracic surgeons preferred the treatment model of surgery plus postoperative chemoradiotherapy nearly ten years ago. Thus, the patients adopting neoadjuvant chemoradiotherapy enrolled in this study is rare (only 9 patients). Given the small

portion of these patients and potential confounders, we excluded these patients in the study. It's better to include these patients in PSM as you advised because PSM could eliminate the confounders between groups. We have included the patients with neoadjuvant chemoradiotherapy and run PSM.

Changes in the text: as shown in Line 134、148, Table 1 and Table 2.

Comment 2: (Patients and Methods, line 82) Why the authors exclude patients who underwent ESD or EMR? Same comments as question number 1.

Reply 2: Thank you for valuable suggestion. Just as neoadjuvant chemoradiotherapy, we excluded patients undergoing ESD or EMR given the small portion of these patients and potential confounders. We think it's better to include these patients in PSM as you advised because PSM could eliminate the confounders. We have included the patients with ESD and run PSM again.

Changes in the text: as shown in Line 152-153, Table 1 and Table 2.

Comment 3: (Results, Table 1/2) What was the proportion of minimally invasive surgery in both group? This is an important issue in esophagectomy, and some papers reported that MIE affects long-term survival. I think the authors should provide the proportion of MIS in both groups.

Reply 3: Thank you for valuable suggestion. Minimally invasive esophagectomy (MIE) could achieve survival rates and reduce perioperative complications, compared with open esophagectomy. We are sorry for this negligence in the study. We have reported the proportion of MIS and included MIE in PSM.

Changes in the text: The proportion of MIS vs open surgery is listed on the Table 1, 2

Comment 4: (Results, Table1/2) I think the extent of lymph node dissection is also important factor for long-term survival and the authors should provide this information and include this factor in PSM.

Reply 4: Thanks for your suggestion. Lymph node dissection during esophagectomy is absolutely a key factor for influencing the prognosis of patients. In our hospital, operation surgeons routinely perform the two-field lymph node dissection for at least 15 lymph nodes (three-field lymph node dissection is performed if necessary). Pathologic N stage usually includes the information of lymph node. To decrease the impacts of lymph node on prognosis, we included pathologic N stage in PSM. We observed that N stage was well balanced after PSM. Therefore, we believe that related bias due to lymph node has been eliminated in our study. We had included pathologic N stage in PSM, which could reflect the information of lymph node.

Changes in the text: None

Comment 5: (Results, Table1/2) Are there any patients who developed chylothorax after esophagectomy? I think authors should provide the percentage of chylothorax after esophagectomy since it is closely related to thoracic duct and its known prevalence is high in esophagectomy patients. Furthermore, if there were any patients who developed chylothorax in non-ligation group, the authors should give information of how they treat chylothorax in these patients. If some patients underwent intervention (eg. thoracic duct embolization) for postoperative chylothorax, I think these patients should be included in ligation group.

Reply 5: Thanks for your question. Postoperative chylothorax is a rare complication after esophagectomy, with an incidence ranging from 0 to 10% as reported [1]. In our study, there are 5 patients (0.82%, 5/609) developed chylothorax after esophagectomy, among whom 3 patients in non-ligation group and 2 patients in ligation group. All three patients in non-ligation group and one patient in ligation group were cured by conservative treatments. One patient in ligation group developed chylothorax after esophagectomy and was underwent reoperation. The sutures used for ligating the thoracic duct were found released and we performed the second thoracic duct ligation. So, the patients with postoperative chylothorax in non-ligation group were cured by conservative treatments and we were not able to include them in ligation group. We have reported the incidence of postoperative chylothorax and some other complications in the paper.

Changes in the text: as shown in Line 156-159.

1. Kranzfelder M, Gertler R, Hapfelmeier A, et al. Chylothorax after esophagectomy for cancer: impact of the surgical approach and neoadjuvant treatment: systematic review and institutional analysis. Surg Endosc 2013; 27: 3530-8.

Comment 6: (Results) Is there any data which could evaluate the long-term nutritional effect of thoracic duct ligation (such as Bwt change)? or blood testing results (e.g. LDL, HDL, TG, chol)?

Reply 6: Thanks for your question. Due to difficulty during follow-up, we did not analyze indicators that are reflective of nutritional status. This was one of the limitation of our study. We did not collect the data concerning the nutritional status during the follow-up.

Changes in the text: None.

Comment 7: (Table 3/4) The authors should provide which gender is set as hazard variable.

Reply 7: Thank you for valuable suggestion. We are sorry for this negligence in the study. We set female as hazard variable.

Changes in the text: as shown in table 3 and table 4.

Comment 8: (Table 3/4) The authors should provide which variable was set as reference in Cox analysis. In pathologic N stage, I think N0 was the reference for the Cox regression analysis, however, there is no information provided.

Reply 8: Thank you for valuable suggestion. We are sorry for this negligence in the study. We have provided which variable is set as reference in cox analysis. We set N0 as hazard variable whose HR value is equal to 1.

Changes in the text: as shown in table 3 and table 4.

Comment 9: Some grammar errors should be corrected throughout the manuscript.

Reply 9: Thank you for valuable suggestion. We have used the AME Editing Service for improving the grammar and syntax. Now we believe that our manuscript has improved a lot. All grammar and syntax errors have been corrected.

Changes in the text: Errors are revised and marked in Red.

Reviewer C

Comment 1: A study by Hou et al is mentioned as the only one raising concerns of a negative effect of prophylactic ligation on survival. Yet, this study is not included in the references. Please provide info.

Reply 1: Thank you for valuable suggestion. The study by Hou et al (1) was the only one concerning the effects of thoracic duct ligation on survival when we designed this study. We are sorry for omitting such an important reference in the manuscript. We have added the important information into the references.

Changes in the text: Reference 8 (line 301)

Reference

(1) Hou X, Fu JH, Wang X, et al. Prophylactic thoracic duct ligation has unfavorable impact on overall survival in patients with resectable oesophageal cancer. Eur J Surg Oncol. 2014;40(12):1756-1762. doi:10.1016/j.ejso.2014.05.002

Comment 2: Overall survival is listed as an endpoint, but it is described as “death due to esophageal cancer” and “All-cause mortality”. Please clarify.

Reply 2: We are sorry for this error. Overall survival means that Patients with a certain disease can die directly from that disease or from an unrelated cause. So it is our negligence to describe it as death due to esophageal cancer. We have re-written it.

Changes in the text: as shown in line 124.

Comment 3: Did the authors have information on nutritional metrics, subsequent hospitalizations, etc. Arguably, overall survival is a very crude metric for the studied variable.

Reply 3: Thanks for your question. The fundamental purpose of this study was to compare the survival difference when we designed the study. Thus, we did not collect other data of the nutritional status, such as weight, ALB, TG, et al. We had intended to obtain overall survival (OS) and disease-free survival (DFS) from the follow-up result but failed. Some family members of patients did not tell the exact death cause (tumor recurrence, metastasis or other disease) of the patients, especially for some elderly patients with comorbidities. Thus, we could not figure out the DFS. As a result, we could only obtain the OS according to the death time of the patients. This is one of the limitations in our study. In addition, we included postoperative complications in the study and described the incidence of each complications. Then Chi-square test was used to compare the difference between LG and NLG.

Changes in the text: as shown in line 155-167.