

Peer Review File

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Reviewer A

Thank you for giving me the opportunity to review this manuscript. The authors showed in a retrospective study that prophylactic bullectomy at the time of esophageal cancer surgery significantly reduced the incidence of postoperative pneumothorax. I think this is very interesting, however, I have some major concerns.

Major:

1) As the authors described, the rate of postoperative pneumothorax development is considered high. I would like to know how many days postoperatively the onset of pneumothorax was common. If a pneumothorax was observed immediately after the operation, the reader might wonder if there was a problem with the intraoperative manipulation.

Reply: We appreciate the review's hard work. The present study showed an 31.19% (n=34) incidence of postoperative pneumothorax after surgery in patients with a definite diagnosis of pulmonary bullae or emphysema, compared to 5.19% in the whole cohort. The mean time of occurrence of postoperative pneumothorax was 3.44 ± 1.68 days (range 1–11 days). And 55.88% of postoperative pneumothorax (n= 19) was observed on 3-5 days after surgery, while only 2 patients presented with pneumothorax on the first day after operation. What's more, all the operations were performed under single-lumen intubation and artificial pneumothorax. Hence, there were almost no intraoperative manipulation involving lung tissue unless adhesiolysis was needed (see Page 8, line 13).

2) The authors stated that the reason for the higher rate of postoperative pneumothorax in their cohort may have been the higher rate of smokers and COPD. However, this may not be considered a compelling reason, as esophageal cancer patients are thought to be more likely to be heavy smokers and have a history of COPD.

Reply: It's a good question. We want to express that, although esophageal cancer patients are thought to be more likely to be heavy smokers and have a history of COPD, the ratio of tobacco use and the proportion of patients with COPD seem higher in our study. For example, there were 44.19% of patients having a history of chronic respiratory disease in our study while only 10.50% of patients (n=285) in previous study (1). Despite smoking and COPD rates were roughly similar to our study, only 101 patients were included in Gillinov et al.'s previous study (2). Future researches based upon larger sample sizes are needed to revise our results.

1. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. *Ann Surg* 2019 Feb;269(2):291-298.

2. Gillinov AM, Heitmiller RF. Strategies to reduce pulmonary complications after transhiatal esophagectomy. *Dis Esophagus* 2017 Nov 1;11(1):43-47.

3) If the rate of pneumothorax complications after esophageal cancer surgery is within the general category (0.79-3.4%), we should be able to deal with pneumothorax when it occurs. It would not be appropriate to adapt the results of a general cohort with different patient backgrounds to the entire population. In addition, it would be medically cost-prohibitive to perform prophylactic bullectomy in all patients who underwent esophageal surgery. The paper would be more interesting if it included a discussion of which cases should be indicated for prophylactic bullectomy.

Reply: The present study showed an 31.19% (n=34) incidence of postoperative pneumothorax after surgery in patients with a definite diagnosis of pulmonary bullae or emphysema, compared to 5.19% in the whole cohort. Therefore, we believe that in esophageal cancer patients with ipsilateral pulmonary bullae (no matter were first discovered in preoperative CT or during surgery), IPB performed in the same anesthesia process is an effective and safe method for the prevention of postoperative pneumothorax, allowing for a shorter postoperative rehabilitation time.

Reviewer B

In this original article, the authors provide the feasibility of initiative pulmonary bullectomy for patients with esophageal carcinoma using a propensity score-matched analysis. The authors reported interesting information, which may have impact on the management for esophageal cancer with ipsilateral pulmonary bullae. There are some comments that are meant to improve the quality of the manuscript.

Major comments

1. There have been previous reports that showed the usefulness of prophylactic bullectomy for esophageal carcinoma. You should show the novelty of your article clearly.

Reply: We appreciate the review's hard work and have revised the paper accordingly (see Page 11, line 6-8).

2. There are cases without COPD. What do the cases have for underlying lung disease?

Reply: In our series, underlying lung diseases mainly consist of chronic obstructive pulmonary disease, bullae, mild pulmonary inflammation presented in CT scan and ground-glass nodules. Most of pulmonary inflammation were accompanied by COPD, hence we did not separate them out in the article. Due to pure GGN less than 6mm, three patients in this study did not undergo nodule resection at same time.

3. Excluding primary spontaneous pneumothorax, almost cases are expected to

have numerous emphysematous changes with unclear boundaries. Therefore, complete excision of these is very difficult. What criteria did you use to select the resected lesions?

Reply: Actually, all the patients included in our study have found definite ipsilateral pulmonary bullae based on intraoperative exploration. The surgical protocol required that the bullas be resected with a sufficient margin and that the team was certain that no residual bullas were present around the staple line. For patients with numerous emphysematous changes with unclear boundaries, the “target regions” were selected using preoperative imaging and intraoperative findings, and the severe emphysematous lung parenchyma (mainly located in the upper and lateral parts of the upper lobe) was resected. The removal of the pulmonary tissues damaged by emphysema was about 25% to 30% volume of the total lung parenchyma.

4. Did you perform the additional procedures such as pleurectomy, mechanical abrasion or covering technique?

Reply: In order to ensure adequate drainage after esophagectomy, we did not perform any additional procedure excepting pulmonary bullectomy.

5. You should show the position during surgery.

Reply: The position during surgery, incisions, esophageal mobilization and dissection as well as mediastinal lymph node dissection were performed essentially as we described in our previous study (1). To achieve the effect of conciseness, we did not explicitly write these above-mentioned contents in current study and you could find in this following article.

1. Guo W, Zhao YP, Jiang YG, et al. Prevention of postoperative chylothorax with thoracic duct ligation during video-assisted thoracoscopic esophagectomy for cancer. *Surg Endosc* 2012 May;26(5):1332-6.

6. You may show the period of development for spontaneous pneumothorax and operation time.

Reply: We have added these related information in the revised full text and Table1.

7. You may show patient backgrounds and surgical results separately.

Reply: We have added separate Table1 into two tables as your suggestion.

8. For multivariate analysis, I think that selecting factors were too many. Considering the number of pneumothorax events, two factors may be reasonable.

Reply: Thank you for this suggestion. We respectfully disagree. In practice, most clinical researchers use multivariate analysis when there are other factors associated with outcome. The reason is that multivariate analysis has become the standard method for proving that there is no confounding. In current study, we have found that except for the significantly linked between bullectomy and a reduced risk of developing pneumothorax, age and FEV1 seem to be in a critical state in univariate

regression analyses. In addition, these factors we selecting are likely involved in the occurrence of postoperative pneumothorax and we also could not rule out the possibility that these factors are potential confounders.

9. Why did you add the factor “pleural adhesion” for analysis. If needed, you may show the reason.

Reply: The presence of pleura adhesion is identified as a significant risk factor for postoperative pneumothorax and prolonged air leak (1,2), which would potentially occur after parenchymal injury during adhesiolysis.

1. Brunelli A, Monteverde M, Borri A, Salati M, Marasco RD, Fianchini A. Predictors of prolonged air leak after pulmonary lobectomy. *Ann Thorac Surg.* 2004 Apr;77(4):1205-10;
2. Kouritas VK, Kefaloyannis E, Tcherveniakov P, Milton R, Chaudhuri N, Brunelli A, Papagiannopoulos K. Do pleural adhesions influence the outcome of patients undergoing major lung resection? *Interact Cardiovasc Thorac Surg.* 2017 Oct 1;25(4):613-619.

10. Why did ipsilateral spontaneous pneumothorax develop after surgery of esophageal carcinoma? You may describe the explanations in Discussion.

Reply: We have added these related content in the revised full text as your suggestion(see Page 9, line 15-16).

Minor comments

1. Abbreviations such as MIE or IPB are not used. You should use appropriately.

Reply: Thank you for the comment. However, as far as we know, MIE is the standard abbreviation of minimally invasive esophagectomy, With regard to IPB and CG, although they were not common abbreviations, all abbreviations in this article have been defined when they are first used in the text. Therefore, we believe that they would not affect readers' correct understanding of the study.

Reviewer C

This study is aimed at the effect of initiative pulmonary bullectomy on the risk of post-operative pneumothorax in patients with esophageal carcinoma.

The content is summarized very well, but I think some revisions are needed.

1. How many patients were detected bullae in preoperative CT? How many patients were first discovered during surgery? please add it to the results and tables.

Reply: We have added these related information in the revised full text and Table1.

Changes in the text: There were 31 patients (77.50%) in IPB group and 53 patients (76.81%) in control group detected bullae by preoperative CT, without a significant difference ($P=1.000$). (see Page 7, line 13-14)

2. About the management of chest drain. How was set up the negative pressure of the drain after surgery? Please describe it.

Reply: Generally, we set up the negative pressure of the drain based on the Three-Compartment System. The three-bottle pleural-drainage system (collection, water seal, and manometer bottles) which forms the basis for contemporary thoracic drainage devices. Nowadays, a suction control chamber is filled to the desired height with sterile fluid (usually 12-20cm H₂O) connected via short tubing to a wall-mounted suction via a regulator set at 2 kPa. Suction drainage is an effective way to deal with persistent air leakage after surgery based on our experience.

3. About the results. How many patients did occur postoperative pneumothorax in each group? I think that it is not match between the number of text and table1. The same is true for discussion (Page9/Line11).

Reply: We appreciate the reviewers' hard work. We are awfully sorry for this clerical error in the article and would like to revise my manuscript immediately.

Changes in the text: However, the present study showed an 31.19% incidence of postoperative pneumothorax after surgery in patients with a definite diagnosis of pulmonary bullae or emphysema, compared to 5.19% in the whole cohort. (see Page 10, line 2)

4. How many staplers did the authors use? If you can, please add it to the results and tables.

Reply: We agree with the reviewer. However, due to absence of the unified writing standard for operative record, stapler-related information was missing in some patients occasionally, especially at the beginning of the study. Future researches based upon more detailed operative records are needed to revise our results.