

## Peer review file

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### Reviewer A

In this retrospective clinical study, the authors demonstrated that there was no significant difference in short-term postoperative outcomes of the resection of anterior mediastinal tumors between the subxiphoid approach and the intercostal approach, and that the right intercostal approach might offer better clinical effect of short-term postoperative recovery for patients than the left intercostal approach. Nowadays, minimally invasive approach such as VATS and Robotic surgery for mediastinal tumors are the major concern for thoracic surgeons. This paper is well-written; however, there are some issues to be overcome.

Comment 1: Figure 1 shows that the total number of minimally invasive surgery for mediastinal tumors was 217 patients; however, in the text, it was 238. Why are these figures different? Besides, what is the real number of subxiphoid approach, 40 or 19? Moreover, after the propensity score matching, what was the number of patients? Please check them carefully before the submission.

Reply: We are sorry to make this mistake. We updated the patient number before submission in manuscript, however, we forget to alter the number in Figure. We fixed this problem in text and figure, please kindly check.

Changes in text: After 1:1 PSM, 19 pairs of patients were collected to evaluate between intercostal and subxiphoid approach, and 81 pairs of patients were collected to compared left and right approach. The baseline characters were well balanced in two groups. (Table 1).

Comment 2: The number of patients included in this study seems relatively small. Why did you do propensity score matching? In my opinion, it was not necessary.

Reply 2: Thanks for your question. We agree your opinion that PSM is not a necessary process. PSM could also be apply in small scale retrospective cohort to balance clinical features [1]. Referring to other reviewers' comments, we would like to retain this part.

Comment 3: The subxiphoid approaches were performed only for anterior mediastinal tumor, right? If so, to compare the subxiphoid approach with the intercostal approach has less impact. Furthermore, to compare the right intercostal approach with the left intercostal approach can be completely another topic. The authors should discuss the topic in another paper.

Reply 3: Thanks for your question. Yes, the subxiphoid approaches were performed only for anterior mediastinal tumor. After PSM, the intercostal approach also only included anterior mediastinal tumor (n=19), thus it is worth to make the comparison, that is also the reason why we conducted PSM in small sample study. In addition, other papers have already explored the comparison between subxiphoid and intercostal approach, the results were similar with this analysis. In this paper, we would like to show a comprehensive analysis of surgical approach, including not only the comparison of subxiphoid and intercostal approach, but also right and left side comparison in the same medical center and the same cohort. It is more valuable and comparative than the comparison in several different studies.

Comment 4: There was no information about the surgical procedures and mediastinal tumors. Did the tumor include thymic cysts? As the surgical procedure, what was the main operation? For example, total thymectomy or tumor resection.

Reply 4: Thanks for your question. We added more detailed information about surgery, please see manuscript.

Changes in the text:

Intercostal approach: Patients are placed in left or right lateral positions depending on the incision approach. A 2-3 cm incision was created initially in the fourth or fifth intercostal space at the anterior axillary line. If the target lesion was located above the confluence of brachiocephalic vein and superior vena cava, or extended thymectomy was needed, an incision on the fourth intercostal space was preferred over the fifth. Two ports were created, one 30-mm port is for surgical approach and a 30 angled camera was placed in the lower lateral 15-mm port.[2] All specimens were safely removed via a specimen bag by enlarging the upper port. Any bleeding or air leak was managed by

reinforcement sutures using 4/0 PROLENE (Ethicon, Somerville, NJ) or application of sealants such as Biopaper (Datsing Bio-Tech Co Ltd, Beijing, China). After the surgery, the closed thoracic drainage tube was placed through the observation hole, and the chest scan examination showed no obvious pleural effusion or pneumatosis. Chest drain was removed when the drainage was less than 200 mL/day. The bedside chest scan could be performed at the same time after the chest tube was removed, and food was resumed after the bowel sound returned to 5 times per minute without nausea or vomiting [3]. Patients who were able to mobilize independently and appeared normal on chest radiography were discharged after chest tube removal.

Subxiphoid approach: The surgical process via mediastinal approach have been already reported elsewhere [4]. A 3-cm incision was made 2 cm below the lower edge of the xiphoid for setting the thoracoscope. Two 5 mm extra pleural thoracic ports were created at the midclavicular line intersecting with the bilateral costal arch to introduce a thoroscopic grasping forceps and a harmonic scalpel. A pneumomediastinum was created by an 8 cm H<sub>2</sub>O positive pressure carbon dioxide (CO<sub>2</sub>) insufflation to enlarge the retrosternal space and facilitate dissection of the tumor. Both the right-sided and left-sided mediastinal pleura were opened. The incision in the chest wall could cause collapse of the lungs. The tumor and surrounding tissue were resected and removed through the subxiphoid port. Finally, the air in the chest cavities was evacuated by inflating the lungs. A drainage tube was inserted into the mediastinum through the subxiphoid incision. If necessary, the process was changed from the subxiphoid approach to the trans thoracic approach or open thoracotomy.

Comment 5: The Discussion part seems redundant. It should be more concise.

Reply 5: Thank you for your suggestion. We re-organized the discussion, please kindly see in manuscript.

## **Reviewer B**

Response: Thank you for your valuable comment, we will fix our manuscript based on your and other reviewers' comments carefully.

Comment 1: Lin.49: “to remove the left and middle mediastinal tumor through the left thoracic approach”. I believe that this must be poorly expressed, because it is complicated to approach a medium mediastinal tumor through the left hemithorax.

Reply 1: Thank you for your comments. The medium mediastinal tumor could be resected from both left and right lateral approach. Our experience told it is easier to do this through right hemi-thorax, with better view. That is one of the aims of this study, we would like to evaluate whether there is a statistical clinical difference between these approaches.

Changes in the text: but a number of literatures have proved that it is feasible and safe to remove the left and middle mediastinal tumor through left lateral intercostal approach

Comment 2: Lin.121: “39 pairs were matched”.

According to fig. 1 should be 19, not 39 . Where is the error??. I get the impression that the error is in fig. 1. However, in tables 3 and 5 they speak again of  $n = 19$ , when in table 1  $n = 39$  for Matched-patients. It is important to review it because the results and the tables do not match.

Reply 2: We are sorry to make this mistake. We updated the patient number before submission in manuscript, however, we forget to alter the number in Figure. We fixed this problem in text and figure, please kindly check.

Changes in the text: After 1:1 PSM, 19 pairs of patients were collected to evaluate between intercostal and subxiphoid approach, and 81 pairs of patients were collected to compared left and right approach. The baseline characters were well balanced in two groups. (Table 1).

Comment 3: Lin.198-209: The authors should make it clear from the beginning of the paragraph that they are going to compare the left and right intercostal approach.

Reply 3: Thank you for your comments. We added this in introduction.

Changes in the text: The left intercostal approach and the right intercostal approach was also compared, as to explore the feasibility and safety of different approaches for the anterior mediastinal tumor resection.

Comment 4: Lin.230-231: “on the long-term quality of life.”

Authors should also consider other limitations related to follow-up: Readmissions, possible relapses,...

Reply 4: Thank you for your comments. We added this information in limitations.

Changes in the text: Further, we did not answer the question whether different approaches would affect relapse time and long-term survival outcomes.

Comment 5: -The authors refer to the pain associated with the approach; however, among the postoperative variables they have not collected any parameters related to pain, it is a pity.

Reply 5: Thank you for your comments. We added the VAS pain score to evaluate the pain status of patients.

Changes in the text: The visual analogue scale (VAS) pain score was lower in patients underwent subxiphoid approach than intercostal group at first post-operative evaluation in 12-24hs (4.36 vs. 2.23;  $P=0.03$ ). The VAS pain score was similar in patients underwent right and left approach at first post-operative evaluation in 12-24hs (4.38 vs. 4.33;  $P=0.63$ ).

Comment 6: -Bibliographic references do not conform to publication standards, including its appearance in the text.

Reply 6: Thank you for your suggestion. We re-organized the manuscript, please kindly check.

## **Reviewer C**

This manuscript discussed the surgical outcome of the anterior mediastinal tumor among three different approaches: subxiphoid, right-side intercostal, and left-side intercostal approach. The authors presented the feasibility of the subxiphoid approach compared to the intercostal approach and the superiority of the right-side intercostal approach compared to the left-side intercostal approach using propensity score-matched analysis. The authors showed that the length of hospital stay was shorter in the right-side approach than in the left-side approach because of less amount of chest drainage discharge and duration of drainage tube placement. This suggestion is very important for the choice of the surgical approach in anterior mediastinal tumor. Furthermore, this manuscript is well written correctly in English.

However, the outcome evaluation of this study is insufficient and invalid. For the most important point, the evaluation of the postoperative pain and quality of life lacked.

Moreover, the authors did not compare the outcome and conduct propensity score-matched analysis among three groups but the authors analysed between each two groups (subxiphoid vs. intercostal approach and the right-side intercostal approach vs. the left-side intercostal approach). We think the authors should conduct a propensity score matching between three groups (subxiphoid, right-side intercostal, and left-side intercostal approach) and evaluate the outcome. This can help thoracic surgeons to select the optimal approach for the anterior mediastinal tumor.

We think this manuscript does not reach the quality of the Journal of Thoracic Disease in this state. However, the comparison of the surgical approach in the anterior mediastinal tumor which the authors described in the present study is very important. So, this paper has a possibility to be published in JTD if these points are improved according to the reviewers' suggestion.

### **Major comments**

Comment 1:

## Methods and Results

The authors should conduct propensity score-matched analysis (PSM) among three groups (subxiphoid, the right-side intercostal approach, and the left-side intercostal approach) and compare the surgical outcome between three groups.

Reply 1: Thank you very much for your comments. We are aiming to compare two different surgical approaches between lateral and subxiphoid approach. Further, within the lateral approach, we tried to observe the clinical difference between right and left group. We regard the two analysis were separated from each other, thus three-group PSM might not suitable for this case.

## Comment 2:

### Results

The authors should add the evaluation for postoperative pain and the amount of administered NSAIDs. As the authors mentioned in Discussion(L170-171), the advantage of subxiphoid approach is the reduction of pain compared to the intercostal approach. So, the evaluation for this is important.

Reply 2: Thank you for your comments. We added the VAS pain score to evaluate the pain status of patients.

Changes in the text: The visual analogue scale (VAS) pain score was lower in patients underwent subxiphoid approach than intercostal group at first post-operative evaluation in 12-24hs (4.36 vs. 2.23;  $P=0.03$ ). The VAS pain score was similar in patients underwent right and left approach at first post-operative evaluation in 12-24hs (4.38 vs. 4.33;  $P=0.63$ ).

## Comment 3:

### Methods

Please clarify the caliper width for PSM in the study.

You should add the caliper width for PSM in the method. We suppose that the optimal caliper width is calculated as follows: a caliper width of “0.2 of the pooled standard deviation of the logit of the propensity score” [Wang Y, Cai H, Li C, et al. Optimal

caliper width for propensity score matching of three treatment groups: a Monte Carlo study. PLoS One. 2013;8(12):e81045. Published 2013 Dec 11. doi:10.1371/journal.pone.0081045].

Reply 3: Thank you for the suggestion. The caliper was set at 0.01 in this paper. Smaller caliper would match more accurate in PSM processing.

Changes in text: The propensity-score matching (PSM) generated from the logistic regression were performed to minimize the differences in confounding variables and facilitate matching patients in the two treatment groups (R software version 2.15.1, <https://cran.r-project.org/>). Variables that could influence the outcomes of treatment were used to generate a propensity score, including Age, BMI, tumor length, gender, tumor position, ASA status and number of comorbidities. Patients were 1:1 matched on the basis of PSM using the nearest-neighbor method on the logit scale. The caliper was set at 0.01. After PSM, standardized mean differences (SMD) before and after PSM were calculated. Confounding variables was considered comparable when SMD below 0.10.

Comment 4:

Methods

Please clarify the variables which you use for conducting PSM (all baseline variables or selected variables).

Reply 4: Thank you for the suggestion. Age, BMI, tumor length, gender, tumor position, ASA status and number of comorbidities were included for PSM. We also added this part in to methods.

Changes in the text: The propensity-score matching (PSM) generated from the logistic regression were performed to minimize the differences in confounding variables and facilitate matching patients in the two treatment groups (R software version 2.15.1, <https://cran.r-project.org/>). Variables that could influence the outcomes of treatment were used to generate a propensity score, including Age, BMI, tumor length, gender, tumor position, ASA status and number of comorbidities. Patients were 1:1 matched on the basis of PSM using the nearest-neighbor method on the logit scale. The caliper was



set at 0.01. After PSM, standardized mean differences (SMD) before and after PSM were calculated. Confounding variables was considered comparable when SMD below 0.10.

Comment 5:

Results

Please clarify the standardized differences for the evaluation of the balance before and after matching. The authors use p-values for the evaluation of the balance; however, this is not sufficient for PSM. The standardized differences is better [Zhang Z, Kim HJ, Lonjon G, Zhu Y; written on behalf of AME Big-Data Clinical Trial Collaborative Group. Balance diagnostics after propensity score matching. *Ann Transl Med.* 2019;7(1):16. doi:10.21037/atm.2018.12.10].

Reply 5: Thank you for the suggestion. We have re-calculated the SD value in this PSM analysis, please kindly check in manuscript.

Changes in the text: The propensity-score matching (PSM) generated from the logistic regression were performed to minimize the differences in confounding variables and facilitate matching patients in the two treatment groups (R software version 2.15.1, <https://cran.r-project.org/>). Variables that could influence the outcomes of treatment were used to generate a propensity score, including Age, BMI, tumor length, gender, tumor position, ASA status and number of comorbidities. Patients were 1:1 matched on the basis of PSM using the nearest-neighbor method on the logit scale. The caliper was set at 0.01. After PSM, standardized mean differences (SMD) before and after PSM were calculated. Confounding variables was considered comparable when SMD below 0.10.

Minor comments

Comment 1:

Introduction

You should change the reference [4] because [4] is a case report. You should refer case-control study including a large number of patients.

Reply 1: Thank you for the suggestion. We changed a reference. Please kindly check.[5]

Comment 2:

Materials and Methods

How did the authors deal with open thoracotomy conversion cases? Please declare this.

Reply 2: Thank you for the question. We only included patients underwent VATS in this study. We added this in manuscript.

Comment 3:

Results L148-149

I think that the length of the hospital stay is too long. Please clarify the reason why it takes so long.

Reply 3: Thank you for the question. The length of stay included the preoperative preparation (necessary examination) and postoperative recovery. We also found it is more meaningful if we only calculated postoperative recovery time. We have changed it in manuscript and Table. Please kindly check.

Comment 4:

Results

Table 5: Coagulation function

I cannot understand the significance of postoperative evaluation for coagulation function. I think the coagulation function does not represent the invasiveness of surgery. I recommend that you declare the inflammatory bio-markers (e.g. CRP and white blood cell count).

Reply 4: Thank you for the question. In our hospital, D-dimer is measured as a routine practice for monitoring the risk of deep vein thrombosis. We will discuss within team according to your suggestion whether it should be a routine practice in the future, thank you. We did not measure inflammatory biomarkers as you mentioned. We also need to discuss this within team. Thank you.

Comment 5:

Results

Figure1, Table 3, 5

You showed that the number of subxiphoid approach is 40 before matching and 39 after matching. However, you declared the number is “19” in Figure1, Table 3, and 5. This is a mistake?

Reply 5: We are sorry to make this mistake. We updated the patient number before submission in manuscript, however, we forget to alter the number in Figure. We fixed this problem in text and figure, please kindly check.

Changes in the text: After 1:1 PSM, 19 pairs of patients were collected to evaluate between intercostal and subxiphoid approach, and 81 pairs of patients were collected to compared left and right approach. The baseline characters were well balanced in two groups. (Table 1).

Comment 6:

Discussion

L181-184

We think the reason for the disadvantage of the subxiphoid approach which was shown as “anatomy, especially posterior segment of upper lobe(S2) and dorsal segment of lower lobe(S6). Secondly, radical lymph node dissection is of difficulty due to the anatomical position of subcarinal lymph nodes(7L)” is not related to the surgery of anterior mediastinal tumor because these procedures are not needed for the resection of it.

Reply 6: Thank you for the comments, we removed this part from manuscript. Thanks again for the detailed review.

Comment 7:

Discussion L204-206

The authors declared in discussion “The less drainage time and hospital stay, the less chance to have a postoperative infection, which is conducive to patients’ rehabilitation and benefit to their lung function.” However, this is a contradiction to the result of Table

3. Between the subxiphoid and intercostal approach, the hospitalization time was tended to be shorter in the subxiphoid approach; however, the drainage of total and the duration of chest tube replacement is longer in the subxiphoid approach although not significant. Please solve the contradiction. I think the most important thing is the control of postoperative pain. So, the results are caused by less pain in subxiphoid approach, I suppose.

Reply 7: Thanks for your question and carefully review again. In order to explain this, we added a pain analysis. We added the VAS pain score to evaluate the pain status of patients. Indeed, the pain score is less in the subxiphoid approach group. Thank you for this advice.

Changes in the text: The visual analogue scale (VAS) pain score was lower in patients underwent subxiphoid approach than intercostal group at first post-operative evaluation in 12-24hs (4.36 vs. 2.23; P=0.03). The VAS pain score was similar in patients underwent right and left approach at first post-operative evaluation in 12-24hs (4.38 vs. 4.33; P=0.63).

#### **Reviewer D**

Comment 1: What was your pre-operative diagnostic investigation? For anterior mediastinal masses a tissue diagnosis is important particularly if there is a high likelihood that the mass may be a lymphoma or a seminomatous germ cell tumor for which surgery is not the initial treatment.

Reply 1: Thank you for the question. Biopsy is not the necessary in our medical center, only these lesions which imaging manifestations were malignant would be considered for a biopsy preoperative, by this way, the lymphoma or a seminomatous germ cell tumor would be confirmed. We also would perform PET-CT for these patients.

Comment 2: In the surgical approaches section, what do you mean by: after the surgery... the chest scan examination showed no obvious.....Is it a Chest-X-ray?

Reply 2: Thank you for the question. Yes, it is Chest-X-ray, we will change this word as you suggest in manuscript. Thank you.

Comment 3: In the data collection section, what is “bilateral t test” ?

Reply 3: Thank you for the question. It is Student t tests and statistical tests were 2-sided. Sorry for this misunderstanding. We have change it in manuscript.

Comment 4: The numbers regarding intercostal and subxiphoid approaches are contradicted in the table and figure 1.(19 or 39?)

Reply 4: We are sorry to make this mistake. We updated the patient number before submission in manuscript, however, we forget to alter the number in Figure. We fixed this problem in text and figure, please kindly check.

Changes in the text: After 1:1 PSM, 19 pairs of patients were collected to evaluate between intercostal and subxiphoid approach, and 81 pairs of patients were collected to compared left and right approach. The baseline characters were well balanced in two groups. (Table 1).

Comment 5: What is the indication for post-operative D-dimer measurement? There is no such indication.

Reply 5: Thank you for the question. In our hospital, D-dimer is measured as a routine practice for monitoring the risk of deep vein thrombosis. We will discuss within team according to your suggestion whether it should be a routine practice in the future, thank you.

Comment 6: The measurement scale of the D-dimer is not mmHg????!!(Result section)

Reply 6: Thank you for the comments, Yes it should be  $\mu\text{g/L}$ , we will fixed it in manuscript. Sorry for this mistake.

Comment 7: In the discussion section, the mentioned limitations for subxiphoid approach are not relevant to this article. They are related to the lung resections ( and not mediastinal tumor resection)

Reply 7: Thank you for the comments, we removed this part from manuscript. Thanks again for the detailed review.

Comment 8: The titles of the tables 3 and 4 are not relevant: “Perioperative period of patients”?? Perhaps they are postoperative issues.

Reply 8: Thank you for the comments, we changed it as “Postoperative recovery”. Please check in manuscript.

Reviewer E

Although I think this paper was relatively well written, strength of the main message of this article may be somewhat weak and the specific mechanisms for the obtained results are unclear. The authors, however, have described and confirmed these points as the limitations. Analyses were done and the results were obtained based on the propensity matching analysis, and the postoperative recovery were assessed by considering the postsurgical coagulation function and the arterial blood gas. These may be considered unique.

Suggested revisions:

Comment 1: Authors should describe how the authors assign the patient to the intercostal group and the subxiphoid group, and the right approach and the left approach in the intercostal group. Did such decisions depend on surgeons’ preferences, some rules in your department (if such exist, please indicate them), or after surgery conference, etc.?

Reply 1: Thank you for the question. Prior to the surgery, anesthetists visited each patient and discussed with surgeons to judge who could be potentially received subxiphoid surgery. The we explain the features of each technique to patients and the

patients would make the decision. So did in the right and left group. We also added this in manuscript.

Comment 2: Please describe the possible reasons which authors consider for the differences the postsurgical coagulation function and the arterial blood gas between the groups. Operation time, postsurgical pain, or other possible specific and scientific reasons.

Reply 2: Thank you for the question. We previously found non-intubated VATS mediastinal tumor resection was associated with lower D-dimer level compared with intubated VATS, which might be potentially explained by ventilation and blood hemodynamic changes between two groups. We just wonder whether it will also be showed difference in each surgical approach, thus we performed this analysis. Detail explanation and mechanism please refer our previous study.[6] (PMID: 31181206) However, we don't regard it as the main results in this analysis, thus we would like to neglect this part in discussion.

Comment 3: Bilateral approach cases were excluded. Please comment these cases in the discussion section. I think that bilateral intercostal approach is needed for patient having myasthenia gravis regardless of with or without the mediastinal tumors. It is important to discuss such patients.

Reply 3: Thank you for the question. We admit that bilateral manner is the important technique in mediastinal tumor resection, however, in order to keep the homogeneity of the study, we excluded these cases. We added this in limitation, please kindly check.

Changes in the text: Fourth, bilateral intercostal approach is needed for patient having myasthenia gravis regardless of with or without the mediastinal tumors, however, in order to keep the homogeneity of the study, we excluded these cases.

Comment 4: From the practical viewpoints, I think it is better to revise followings: 83.19% -> 83.2%, 16.81% -> 16.8%, 312.1 ml -> 312 ml, and 193.9 ->194 ml, in the abstract section and the relevant parts.

Reply 4: Thank you for the valuable suggestion. We have fixed these data in manuscript, please kindly check.