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Comment 1: \*\*\*\*\*

Reply 1: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

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Reply 2: \*\*\*\*\*

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## Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-20-6125>

### Reviewer A

Correct writing errors

The article on the study carried out is worth publishing. However, I did find some writing errors. Only the abstract is available and I did not have access to the full text.

The claim that the technique “can be used as an alternative when intubation is not available. “ may be not valid.

**Reply:** Thanks for your comments and valuable suggestion. We have polished and fixed the language error, thank you very much.

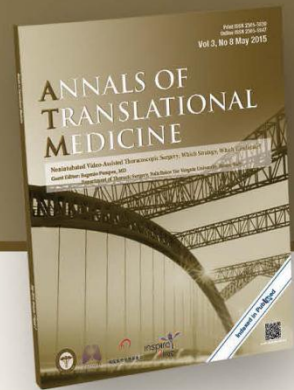
**Changes in the texts:** Please refer in manuscript.

### Reviewer B

Dear authors,

Thank you for the opportunity to review the manuscript "Non-Intubated Anesthesia Video-Assisted Thoracic Surgery for Subxiphoid Anterior Mediastinal Tumor Resection” for the Annals of Translational Medicine.

The authors reviewed clinical data of 40 patients, who received surgical treatment for mediastinal mass. For the whole cohort subxiphoid approach was used and the individuals were divided into two groups. One group underwent anesthesia with regular intubation with double-lumen-tube and one group underwent anesthetic management without endotracheal intubation and without application of muscle relaxant.



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Reply 2: \*\*\*\*\*

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The authors present interesting results and the whole manuscript is very well structured. This survey displays the feasibility and safety of non-intubated subxiphoid VATS for mediastinal mass. Grammar and syntax are very fine and the manuscript is legible. The STROBE criteria are fulfilled.

**Reply:** Thanks for the positive comments.

The conclusion is realistic and directly derived from the results. Unfortunately, the groups are too small to receive significant results for difference in complications rates.

**Reply:** Thanks for your valuable comments. We admitted that the small sample size might affect the statistical significance, and we added this in imitation (discussion). The morbidity of the anterior mediastinal tumor was low and subxiphoid surgery was not a routine practice in thoracic surgery; this study reported a preliminary exploration on non-intubated subxiphoid VATS for mediastinal tumor, with the aim to confirm its feasibility. According to this target, this study has achieved the goal.

**Change in text:** The morbidity of the anterior mediastinal tumor was low and subxiphoid surgery was not a routine practice in thoracic surgery; this study reported a preliminary exploration on non-intubated subxiphoid VATS for mediastinal tumor, with the aim to confirm its feasibility. According to this target, this study has achieved the goal.

Patient selection is mandatory in studies to evaluate feasibility of a procedure, but there is a bias when anesthesia performs selection for the procedure.

**Reply:** Thanks for your valuable comments. We admitted your comments that when non-intubated anesthesia was performed, there were several restriction for patient selection. For example: BMI  $\leq$  30, good heart and pulmonary function, etc. However, we compared the baseline characteristics of I-VATS and NI-VATS, finding no significant difference, thus we don't apply the propensity score matching in this study.



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Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

The authors have to correct the figures. The figures and the legends does not fit to the description in the text.

**Reply:** Thanks for your valuable suggestion. We checked all figures and legends and fixed the inconsistency.

**Change in text:** Please refer to Figure 1 and Figure 2.

In conclusion: You cover an interesting topic with good results and the whole manuscript is well thought out.

**Reply:** Thank you again for all valuable comments.

## **Reviewer C**

This article is interesting but some questions and comments are necessary.

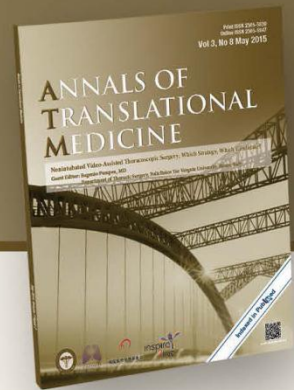
1) In the title. After anesthesia the word “for” is probably missing

**Reply:** Thanks for your valuable suggestion. We admitted your advice. We think that deleting the “anesthesia” might be better.

**Changes in the texts:** Non-Intubated Video-Assisted Thoracic Surgery for Subxiphoid Anterior Mediastinal Tumor Resection

2) Line 63. indication to perform subxiphoid VATS resection for anterior mediastinal. Can the location of the nodule in the upper third of the anterior mediastinum influence the decision making ?

**Reply:** Thanks for your question and comments. If the tumor is located at the thoracic inlet, the transcervical approach was selected. But we did not tried the non-intubated at this condition. We will add this condition in method and discussion.



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Reply 2: \*\*\*\*\*

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**Change in text:** When the tumor located at the thoracic inlet, the transcervical approach was selected. Migliore et al. has described their experience in single incision extended video assisted transcervical thymectomy and demonstrated that this be a safe and successful procedure. However, we have not tried such procedure under non-intubated anesthesia.

1) Migliore M, Criscione A, Nardini M, Patti F, Borrata F. Single incision extended video assisted transcervical thymectomy. J Vis Surg. 2017;3:154. Published 2017 Oct 28.  
doi:10.21037/jovs.2017.10.06

3) When intubation is not available ?

COMMENT: What does it mean? Could you explain better ?

**Reply:** Thank you for the question. The reason for difficult intubation could be divided into three types: anatomical variation (airway deformity, short neck), space-occupying lesions (tumor, bleeding) and medical factor (Unskilled intubation).

4) Chest tube duration was shorter in NI-VATS group

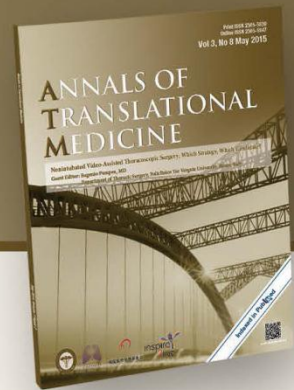
COMMENT: 1.81 vs 1.84 does not seems to be difference. Could you please control your data ?

**Reply:** Thank you for pointing out this mistake. We recalculated the P value and fixed the mistake, p=0.08.

**Change in text:** The anesthesia time (231.76 vs 244.71 min; p=0.218), the operation time (152.35 vs 143.64 min; p=0.980), chest tube duration (1.81 vs 1.84 day; p=0.08), the total volume (351.95 vs 348.00 ml; p=0.223), post-operative pain scores (2.79 vs 2.93, P=0.413) and the length of stay (9.47 vs 10.57 day; p=0.970) were all comparable between two groups.

5) Line 98 Conventional median sternotomy is considered the standard practice

COMMENT: I disagree as median sternotomy is almost never used for mediastinal diseases except for large tumors so probably it sounds better that conventional median sternotomy was considered



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Reply 1: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

**Reply:** Thank you for pointing out this. We admit your point of view and change the description.

**Change in text:** Conventional median sternotomy is considered as the standard therapy in last century, but video-assisted thoracic surgery (VATS) has gradually taken the place in decades.

6) the length of stay (9.47 vs 10.57 day;  $p=0.970$ ) were all similar between the two NI-VATS and I-VATS group.

COMMENT: why the length of stay is so long if the drain has been removed after 1,8 days. Could you explain ?

**Reply:** Thank you for pointing out this. The length of stay included time before and after surgery. In average, 3-5 days are needed to finish pre-operative examination before surgery.

7) Chest tube duration was shorter in NI-VATS groups (1.81 vs 1.84 day;  $p=0.008$ ),

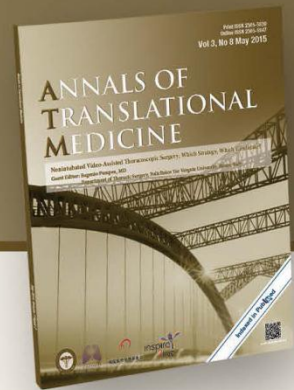
COMMENT: I am not sure that there is difference in the duration of thoracic drainage as you are showing  $p=0.008$  !

**Reply:** Thank you for pointing out this mistake. We recalculated the P value and fixed the mistake,  $p=0.08$ .

**Change in text:** The anesthesia time (231.76 vs 244.71 min;  $p=0.218$ ), the operation time (152.35 vs 143.64 min;  $p=0.980$ ), chest tube duration (1.81 vs 1.84 day;  $p=0.08$ ), the total volume (351.95 vs 348.00 ml;  $p=0.223$ ), post-operative pain scores (2.79 vs 2.93,  $P=0.413$ ) and the length of stay (9.47 vs 10.57 day;  $p=0.970$ ) were all comparable between two groups.

8) The authors wrote: Not using muscle relaxants is benefit for myasthenia gravis patients. but only 4 patients had MG and 15 out 40 had thymomas.

COMMENT: how many thymectomy did you performed ? Moreover have you been able to perform extended thymectomy ? Do the authors think that extended thymectomy could be performed under with the patient awake ? A comparison with another "non intercostal access"



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Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

surgery for the mediastinum such as single incision extended transcervical thymectomy should be discussed (1).

**Reply:** Thank you for the question. Sure, we have done the thymus horns and the perihilar fat in thymoma patients with MG between the phrenic nerves at both sides in NI-VATS and I-VATS group. When dissecting fat, surgeons need to be careful not to injure the phrenic nerves. After vagus nerve blocked by lidocaine, the cough almost disappeared. For mediastinum moving, little dose of cis-atracurium would significant reduce it. We added this in discussion. All patients were sedative with propofol, we did not perform the awake anesthesia.

If the tumor is located at the thoracic inlet, the transcervical approach was selected. But we did not tried the non-intubated at this condition. We will add this condition in method and discussion.

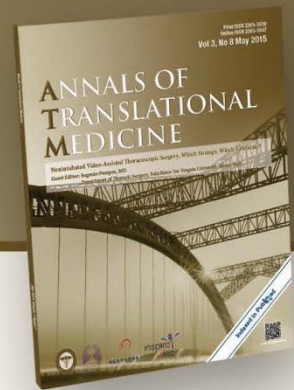
**Change in text:**We have done the thymus horns and the perihilar fat in thymoma patients with MG between the phrenic nerves at both sides in NI-VATS and I-VATS group. When dissecting fat, surgeons need to be careful not to injure the phrenic nerves. After vagus nerve blocked by lidocaine, the cough almost disappeared. For mediastinum moving, little dose of cis-atracurium would significantly reduce it.

When the tumor located at the thoracic inlet, the transcervical approach was selected. Migliore et al. has described their experience in single incision extended video assisted transcervical thymectomy and demonstrated that this be a safe and successful procedure. However, we have not tried such procedure under non-intubated anesthesia.

1) Migliore M, Criscione A, Nardini M, Patti F, Borrata F. Single incision extended video assisted transcervical thymectomy. J Vis Surg. 2017;3:154. Published 2017 Oct 28. doi:10.21037/jovs.2017.10.06

9) Another point of discussion could be the position of the mass/nodules.

The location in the upper third probably suggest a transcervical approach. Could the authors add few comments in the discussion ?



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Changes in the text: \*\*\*\*\*

Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

**Reply:** Thanks for your question and comments. If the tumor is located at the thoracic inlet, the transcervical approach was selected. But we did not tried the non-intubated at this condition. We will add this condition in method and discussion.

**Change in text:** When the tumor located at the thoracic inlet, the transcervical approach was selected. Migliore et al. has described their experience in single incision extended video assisted transcervical thymectomy and demonstrated that this be a safe and successful procedure. However, we have not tried such procedure under non-intubated anesthesia.

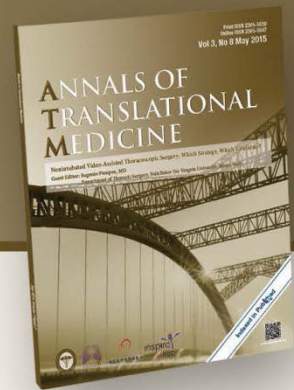
1) Migliore M, Criscione A, Nardini M, Patti F, Borrata F. Single incision extended video assisted transcervical thymectomy. J Vis Surg. 2017;3:154. Published 2017 Oct 28.  
doi:10.21037/jovs.2017.10.06

Thank you for sending this paper to ATM

## Reviewer D

I am sorry to disappoint you but I suggest the authors to clarify the following questions before you come to a conclusion. I understood that you wanted to demonstrate the feasibility of non-intubated video-assisted thoracic surgery for subxiphoid anterior mediastinal tumor resection. The question is how many patients you have completed the operations? 21 or 19? If the cases were too limited, it would be better for you to show the outcomes of NIVATS group as a case series.

**Reply:** Thank you for the question. As we mentioned in manuscript, a total of 40 patients between December 2015 and September 2019 underwent subxiphoid VATS anterior mediastinal tumor resection were consecutively included in this analysis. Among them, 21 patients received NI-VATS (52.5%) and 19 patients were treated under I-VATS (47.5%). We acknowledged the sample size is small, and we added this in limitation. We aim to explore whether NI-VATS is a proper technique, thus the comparative study was conducted.



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Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

**Change in text:** The morbidity of the anterior mediastinal tumor was low and subxiphoid surgery was not a routine practice in thoracic surgery; this study reported a preliminary exploration on non-intubated subxiphoid VATS for mediastinal tumor, with the aim to confirm its feasibility. According to this target, this study has achieved the goal.

Method:

Line 129-132

Figure 1, 40 patients signed the consent? For agreement or refusal of NIVATS?

**Reply:** Thank you for the question. All patients has signed the consent for all procedure, including the surgery types, anesthesia types, etc.

Line 137-139 should be moved to line 130. It indicated how the patients were got from each group.

**Reply:** Thank you for the comments. We have changed it as your suggestion.

**Changes in the texts:** All patients met the criteria were asked whether they would like to receive new technique of NI-VATS, patients who refused would get the conventional intubated surgery.

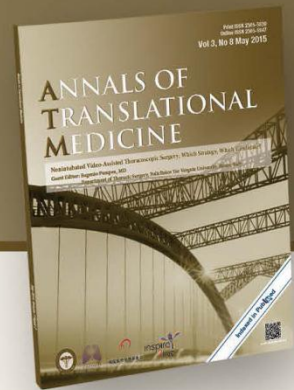
The figure 1, the exclusion of 219 cases should be positioned from 259 cases but not from the 40 cases you studied.

**Reply:** Thank you for the comments. We have changed it as your suggestion.

**Changes in the texts:** Please refer the figure 2.

Line 199-204, how many patients in each group you have put into comparison? NIVATS vs IVATS: 21 vs 19? Or 19 vs 15? As your title focused on Subxiphoid approach, patients receiving transthoracic or sternotomy should be excluded from the comparisons. It would be better for our readers if you make the tables, the postoperative outcomes clear for subxiphoid





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approach or for all the patients. However, I do not think it is appropriate to compare all the patients with different approaches. The postoperative pain, the need of retained chest tubes may be quite prolonged for different approaches.

**Reply:** Thank you for the comments. A total of 40 patients between December 2015 and September 2019 underwent subxiphoid VATS anterior mediastinal tumor resection were consecutively included in this analysis. Among them, 21 patients received NI-VATS (52.5%) and 19 patients were treated under I-VATS (47.5%). Comprehensive data of 31 patients (17 NI-VATS, 14 I-VATS) were available for the post-operative pain score analysis.

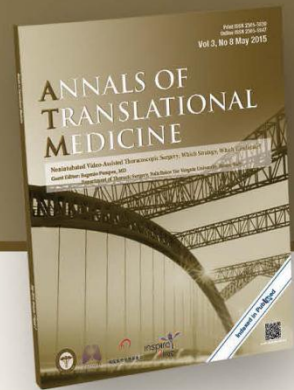
We agree with you so much on the idea of comparison for different approaches, and we have published a paper recently about this topic (*Mao Y, Lan Y, Cui F, Deng H, Zhang Y, Wu X, Liang W, Liu J, Liang H, He J. Comparison of different surgical approaches for anterior mediastinal tumor. J Thorac Dis 2020. doi: 10.21037/jtd-20-266*). This study demonstrated that subxiphoid approach is associated with less pain compared with intercostal approach. The right intercostal thoracic approach may offer better clinical effect of short-term postoperative recovery. We have added this in discussion.

**Change in text:** One of our recent work demonstrated that subxiphoid approach is associated with less pain compared with intercostal approach. The right intercostal thoracic approach may offer better clinical effect of short-term postoperative recovery.

## Reviewer E

Dear authors

you report the first comparative series of intubated and non-intubated subxiphoidal VATS resection of anterior mediastinal tumor. The patient number is remarkable regarding the novelty of the technique. The novelty is the reason why I have some remarks, and I hope for more information in a revised manuscript:



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Changes in the text: \*\*\*\*\*

Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

Major issues:

Language: needs thorough correction of typography, wording and grammar by a native speaker or a professional service.

**Reply:** Thanks for your comments and valuable suggestion. We have polished and fixed the language error, thank you very much.

**Changes in the texts:** Please refer in manuscript.

Methods:

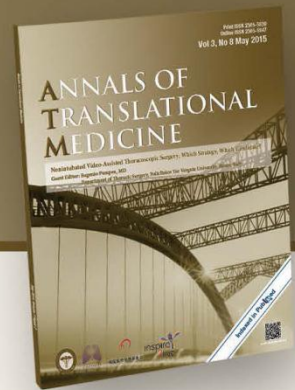
- You report mainly the surgical in- and exclusion criteria. According to your report, it was to the anaesthetist's discretion to whom NI-VATS was offered. Please report the anaesthesiologic criteria (for example, Mallampati score, etc.).

**Reply:** Thanks for your comments and valuable suggestion. Surgical anesthesia criteria:

Exclusion criteria: cases that underwent median sternotomy, cases that underwent trans thoracic approach surgery, malignant cases with obvious invasion to the surrounding organs. We have also described the anesthesia criteria in the method part, please kindly check. Contraindications to NI-VATS (Anesthesia criteria): American Society of Anesthesiologists (ASA) class 3 or greater, body mass index (BMI) 30 or greater, severe heart disease (e.g., ischemia, arrhythmia, etc.), hemodynamic instability, coagulopathy, asthma and sleep apnea syndrome.

- When NI-VATS patients had to be converted to sternotomy or transthoracic approach, I assume that anaesthesia was also converted to intubation. Please report the anaesthetist's preparations for a possible switch to intubation and how it was performed (for example, intubation through the laryngeal mask?).

**Reply:** Thanks for your questions and valuable suggestion. If hypoxemia or hypercapnia or other indicated conditions for conversion occur during the surgery and cannot be resolved after



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non-invasive management, the anesthesiologist must be able to switch the anesthesia mode and perform tracheal intubation. The single lumen endotracheal tube is preferred.

The single-lumen tube should be inserted under the guidance of a fiber optic bronchoscope when the patient is in a lateral position, which is more difficult than normal practice. To achieve this a small pillow should be placed under the head to allow the front, bottom perspective of the mouth and nose to stay up and the head and neck should be parallel to the central axis of the body.

**Change in text:** If hypoxemia or hypercapnia or other indicated conditions for conversion occur during the surgery and cannot be resolved after non-invasive management, the anesthesiologist must be able to switch the anesthesia mode and perform tracheal intubation. The single lumen endotracheal tube is preferred.

The single-lumen tube should be inserted under the guidance of a fiber optic bronchoscope when the patient is in a lateral position, which is more difficult than normal practice. To achieve this a small pillow should be placed under the head to allow the front, bottom perspective of the mouth and nose to stay up and the head and neck should be parallel to the central axis of the body.

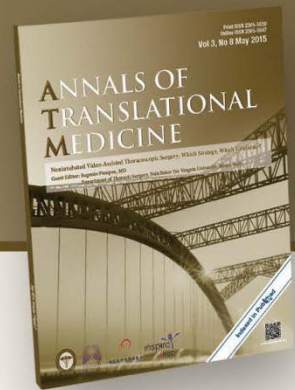
## Results

Your most interesting patients are those with thymoma. Although this subgroup is too small for comparative calculations, could you provide some more descriptive information, at least in supplemental table? Masaoka, WHO-type, number of lymphnodes excised, etc.?

**Reply:** Thanks for your questions and valuable suggestion. The histology of thymoma was summarized in Table 1, please kindly refer.

## Discussion

As the technique is new and challenging for the surgeon, you should share some of your experiences, besides solely interpreting your data. For example, in thymoma, the surgeon should attempt to reach both thymus horns and the perihilar fat; did you manage it in your NI-VATS



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thymoma patients? How did you deal with coughing? You discuss vagus block (l. 263), but did you use it?

**Reply:** Thank you for the question. Sure, we have done the thymus horns and the perihilar fat in thymoma patients with MG between the phrenic nerves at both sides in NI-VATS and I-VATS group. When dissecting fat, surgeons need to be careful not to injure the phrenic nerves. After vagus nerve blocked by lidocaine, the cough almost disappeared. For mediasdinum moving, little dose of cis-atracurium would significant reduce it. We added this in discussion.

**Change in text:** We have done the thymus horns and the perihilar fat in thymoma patients with MG between the phrenic nerves at both sides in NI-VATS and I-VATS group. When dissecting fat, surgeons need to be careful not to injure the phrenic nerves. After vagus nerve blocked by lidocaine, the cough almost disappeared. For mediasdinum moving, little dose of cis-atracurium would significantly reduce it.

Please provide some pre- and intraoperative physiological data (for example, lung function, intraoperative hypoxaemia and hypercapnia). If not, you should at least discuss it as a limitation.

**Reply:** Thank you for the question. The pre-operative lung function (FVC, FEV1) was summarized in Table 1, please kindly refer. The intraoperative hypoxaemia and hypercapnia were not recorded, and we added this in limitation as your advice.

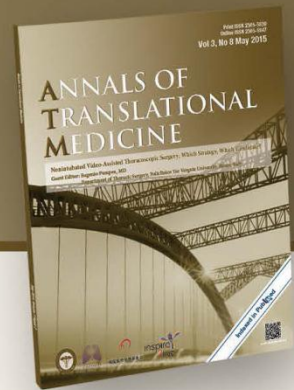
**Change in text:** In addition, lack of intra-operative ventilation information (hypoxaemia and hypercapnia), hindering our further understanding on perioperative pneumodynamics.

Minor issues

Methods

- ll 173-174: How come you used more propofol in NI-VATS in the anaesthesia maintenance than in the I-VATS group?

**Reply:** Thank you for the question. Large among of propofol would stop the shallow anesthesia and spontaneous ventilation, thus the usage of propofol in NI-VATS group is less than I-VATS.



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Changes in the text: \*\*\*\*\*

Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

## Results

- ll. 205-206: you write NI-VATS twice, where you obviously meant to compare NI-VATS to I-VATS.

**Reply:** Thank you for pointing out this mistake. We have fixed this point.

**Change in text:** The incidence of post-operative complication was less in the NI-VATS group

- ll. 213: chest tube duration 1.81 vs 1.84,  $p=0.008$  --> this p seems unlikely in 40 patients. Are you sure, p was calculated correctly here? Which were the standard deviations? Which test did you use?

**Reply:** Thank you for pointing out this mistake. We recalculated the P value and fixed the mistake,  $p=0.08$ .

**Change in text:** The anesthesia time (231.76 vs 244.71 min;  $p=0.218$ ), the operation time (152.35 vs 143.64 min;  $p=0.980$ ), chest tube duration (1.81 vs 1.84 day;  $p=0.08$ ), the total volume (351.95 vs 348.00 ml;  $p=0.223$ ), post-operative pain scores (2.79 vs 2.93,  $P=0.413$ ) and the length of stay (9.47 vs 10.57 day;  $p=0.970$ ) were all comparable between two groups.

## Conclusion

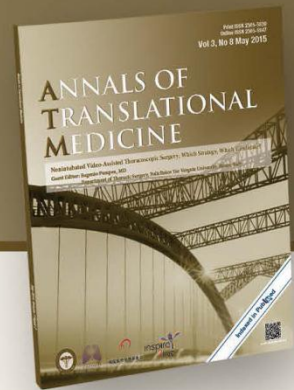
1. 289 It should be emphasized (for readers in a hurry) that NI-VATS is a safe and technically feasible option "in selected patients".

**Reply:** Thank you for the suggestion. We added the selected patients in abstract and conclusion.

**Change in text:** In summary, this study reveals that NI-VATS mediastinal tumor resection is a safe and technically feasible option in selected patients.

Points I like very much:

- novelty and sample size
- report of pain scales and analgesic medication
- apart from muscle relaxation, the anaesthetic medication was equivalent in both groups.



**Notice:** Please give your response to the comments point-by-point as shown in the following format.

【At the END of each reply/response from you, please DO describe how you responded to the reviewer comment in the text, e.g., "we added some data ...(see Page xx, line xx)" or "we have modified our text as advised (see Page xx, line xx)"】.

Comment 1: \*\*\*\*\*

Reply 1: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

Comment 2: \*\*\*\*\*

Reply 2: \*\*\*\*\*

Changes in the text: \*\*\*\*\*

- the explanation why and how you used SIMV to manage the problems of the bilateral pneumothorax.

**Reply:** Thank you for highlighting these points in this study. We hope to offer a new surgical choice for patients with anterior mediastinal tumor.

## Reviewer F

Congratulation to this pioneer work. My questions are as follows:

1. Is there any tumour size limit for the subxyphoid resections?

**Reply:** Thank you for the question. No restriction was set for the tumor length in this study. However, patients underwent sternotomy and cases with obvious invasion to the surrounding organs were excluded. These cases might be associated with larger tumor size than the population in this study.

2. Did you use BIS in case of NI-VATS?

**Reply:** Thank you for the question. BIS was only used in I-VATS.

3. Could you mention the histology of the thymoma?

**Reply:** Thank you for the question. The histology of thymoma was summarized in Table 1, please kindly refer.

4. Is the sentence finished in the row 251?

**Reply:** Thank you for the comment. We have fixed this sentence, please kindly check.

**Change in text:** The present study indicated that NI-VATS under subxyphoid approach was a feasible procedure with similar intraoperative and postoperative outcomes with conventional I-VATS group.