

Peer Review File

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First-Round Peer Review

Reviewer A

I would like to congratulate the author of an interesting article entitled “Analyzing the Impact of Minimally Invasive Surgical Approaches on Post-Operative Outcomes of Pneumonectomy and Sleeve Lobectomy Patients”.

The article is written in good-quality English, but I believe that it requires significant corrections.

Comment 1: Abstract.

a. The abstract is too extensive. I propose reducing the amount of text, especially in the introduction.

Reply: Thank you for this comment. We have shortened the abstract.

Location: Abstract

b. In the abstract, “Background” instead of “Introduction” should be used, according to the JTD guidelines.

Reply: Thank you for suggesting this. We have made the adjustment.

Location: Abstract

c. "P" values should be provided to three decimal places in all cases, for example $p = 0.034$ or $p < 0.001$.

d. I suggest not using newly created abbreviations (“SL” and “PN”) in the abstract.

Reply: Thank you for the suggestion. We have taken the abbreviations out.

Location: Abstract

Comment 2: The introduction is very well written and requires no corrections.

Reply: Thank you

Comment 3: The methodology section should include the information on Bioethics Committee’s approval of the study or waiver of the approval, as it was a retrospective trial.

Reply: Based on the retrospective nature of this review the authors did not seek Bioethics Committee approval prior to gathering data.

Comment 4: Results:

a. The "Results" are written in pretty language, but they contain a large amount of irrelevant information, which makes it difficult to extract important information from

the text. I propose to present only the most essential information, while the remaining information should be included in tables. As a general rule, the same information should not be repeated in the text and in tables. Information regarding the sex, age, stage, histology, complications and recurrence are included in tables and should be removed from the “Results” section. I propose to include only brief information here, for example: “The baseline and surgical characteristics are listed in Tables 1 and 2, respectively.”

Reply: Thank you for these suggestions. We have edited the methods section to make it more abbreviated.

Location: Results

b. Values for TNM stage I/II/III for PN and SL do not add to the number of patients in each of the groups, and percentages do not add to 100%; this information is crucial for the type of the study that evaluates long-term survival.

Reply: Thank you for finding this. We have edited the table and re-tabulated the totals.

Location: Table 1

c. "P" values should be provided to three decimal places in all cases, for example $p = 0.034$ or $p < 0.001$.

Reply: Thank you for this suggestion. We have edited the p values.

Location: Abstract and Results

d. Were there any differences between the TNM stages in PN and SL group? And between surgical risk in each group? I suggest using some risk-assessment scale, like ThRCRI, Eurolung1 and Eurolung2. Currently, many authors use propensity score matching to address selection bias.

Reply: Thank you for these comments. We have changed our Table 1 and therefore your initial question will no longer lead to confusion. The authors believe that for this study using a risk-assessment scale like those you suggested would not add merit to our results.

e. I think, that sample size is too small and too varied to allow for the analysis of long-term results.

Reply: Thank you for this discussion point. We hope that by publishing this work we will encourage more surgeons to perform SL and PN using a VATS approach. We agree that our sample size in this study is small but we believe it is still impactful to the field. In particular we know that the SL numbers are small but not many people perform this operating so this work has the potential to encourage others to adopt this approach.

Comment 5: Discussion

a. I suggest using “was related” instead of “leads”, because retrospective studies in

general do not allow to assess causality.

Reply: We agree with this statement and have altered the sentence as you suggested.

Location: Discussion

b. 30- and 90-day mortality of pneumonectomy was relatively high compared to the studies cited in the manuscript. How do authors explain this?

c. Was there any chronological bias?

Reply: Thank you for this question. Due to the relative novel-ness of the VATS SL we expect that there was chronological bias. The rates on VATS PN stayed relatively constant through the study but there were slightly more operation done using a VATS approach during the final year.

Comment 6: Tables require extensive changes. Values in Table 1: TNM stage I/II/III for PN and SL do not add to the number of patients in each of the groups. In addition to the number of patients, % should be added. A short description below each table should be included, for example: “Data are expressed as numbers, means \pm standard deviations, or medians with interquartile ranges (IQRs)”, “Statistical significance: $p < 0.05$ ”. Differences for each variable should be analyzed and p value should be included in additional column.

Reply: Thank you for these suggestions. We have altered the tables in the suggested ways.

Location: Tables

Reviewer B

In this study, the authors evaluated the benefits of lobectomy with bronchoplasty compared to those of pneumonectomy and investigated whether minimally invasive approaches to these procedures would impair treatment outcomes. However, owing to the limitations of this study, which include single-center, few cases and retrospective researches, the background of the two groups being compared was not uniform.

Comment 1: In the Methods section, the author must specify the surgical procedure for each operation performed at the author’s institution.

Reply: Thank you for this suggestion. We have added procedural information in the methods section.

Location: Methods

Comment 2: In addition, it is necessary to describe the details of the selection criteria for each surgical procedure and clarify whether it is possible to compare the cases analyzed in this study.

Reply: Thank you for this suggestion. Due to the retrospective nature of this study it is not possible to know the exact reasons the surgeon had for doing one

procedure rather than another. This could have been based on a number of factors including patient preference that are not available retrospectively.

Comment 3: Postoperative pathological examination results, such as tumor invasion into the bronchial stump and TNM classification (including not only the stage but also the result of each factor), should also be presented. The sum of each variable does not match the total number shown in the table, for example, in stage or distant recurrence cases in sleeve-lobectomy.

Reply: Thank you for this advice. We have edited and fixed the tables in the suggested ways. We have edited Table 1 so that there should no longer be ambiguity about pathologic stage.

Location: Tables

Comment 4: Among surgical complications, the incidence of postoperative complications requiring invasive treatment is high, especially in pneumonectomy with VATS, including three cases of empyema, four of bronchial stump fistula, eight of pneumonia, and six of recurrent nerve palsy.

Reply: Thank you again for taking the time to read our work and contribute comments. The data that you have presented are what we found when retrospectively reviewing our records. Following the complications persons involved in the surgical care and recovery of the patients analyzed reasons for the complications and tried to mitigate conditions that lead to the occurrences.

Comment 5: The authors conclude that the minimally invasive approach does not compromise long-term survival, but can this procedure become standard?

Reply: Thank you for this question. We do believe that VATS Pneumonectomy and Sleeve Lobectomy can become standard practice. We believe that the benefits to the patients out-weigh the negatives of approaching these operations minimally invasively. We hope that wider spread adoption of these procedures occurs in the coming years.

Comment 6: Finally, numerous non-standard, inexplicable abbreviations that are difficult to understand were used.

Reply: Thank you for pointing this out to us. We have reviewed the manuscript and removed abbreviations that are not widely accepted.

Comment 7: In addition, the Introduction section should concisely show the facts that support the purpose of this study and avoid duplication.

Reply: We have rewritten the introduction following this comment as well as other reviewers' suggestions. Thank you for the advice.

Location: Introduction

Reviewer C

The authors of the manuscript report a retrospective review of patients undergoing SL or PN, via thoracotomy or thoracoscopy. Nitsche and colleagues describe a cohort of 108 patients who matched their inclusion criteria, and derived survival conclusions from KM analysis, in addition to a multivariate model. The current manuscript requires significant additions in order to ensure appropriateness in the conclusions drawn. While the authors report a novel and interesting comparison between two heterogeneous groups of patients undergoing resection for NSCLC, the analysis lacks the incorporation of patient-related factors such as performance status, or pulmonary function tests, that undoubtedly have a role in patient selection for these operations, and for these approaches.

Additionally, I recommend the authors address the following major comments prior to consideration for publication.

a) Major Comments

Comment 1: The abstract is misleading. I would strongly encourage the authors to describe the sample size according to the analysis they report. The authors should include sample size of the subgroups (VATS SL, VATS PN, ect), as they report (wrongly) the results of their multivariate analysis (p value do not match table 5, resection should read $p < 0.001$, and stage should read exact p value, it would be worthwhile to add the p value of approach as well).

Reply: Thank you for these suggestions. We have edited the abstract, added the size of the groups and fixed the p values.

Location: Abstract and results

Additionally, the conclusion that VATS approach was found to be non-inferior to open surgical approach is incorrect as the authors have compared two largely different groups of patients (SL and PN). Without MVA Odds Ratio confidence intervals, it is incredibly difficult to believe that a p value of 0.053 can be categorized as “non-inferior.” Particularly without a sample size calculation that permits a non-inferiority analysis. Additionally, considering a nearly significant p value, with an odds ratio of 1.75, I imagine the 95CI to be relatively wide, further confirming the heterogeneity in this cohort.

Reply: Thank you very much for this comment and discussion. We hope that our sample size will grow much larger as more thoracic operation are being done in a minimally invasive fashion. We admit that our sample size is small, particularly our VATS SL group. We still believe that our data is important and show the feasibility of continuing to integrate MIS into thoracic surgery. This study supports the wider adoption of VATS despite the small sample size.

Comment 2: Multivariate and analysis is missing patient factors, such as performance status, as might be represented by Zubrod status, or CDS. Without the addition of performance status, the analysis comparing outcomes lacks appropriate adjustment. This is particularly relevant, as the authors stated in their introduction that operative

decision making between SL and PN requires patient characteristics. Perhaps, the authors can also add results of PFTs (FEV1, FVC) in their multivariate model.

Reply: Thank you for these comments. Due to the retrospective nature of this study many of the suggested variables are not available to be gathered. When discussed among authors we did not feel that their absence significantly subtracted merit from our analysis.

Comment 3: Define whether the KM analysis reports disease-specific or overall survival, I would recommend using disease-specific survival in this context.

Reply: Thank you for this comment. This was DSS and we have edited the result section to specify.

Location: Table 1; results

Comment 4: I would recommend reporting survival in months rather than days

Reply: Thank you for this suggestion. The authors believe that a greater change can be seen when the data is analyzed using days. We believe this scale better illustrates our point.

Location: figure 1

Comment 5: Lines 122-124: The authors report a study performed previously (and at citation position 20 in the current manuscript) describing outcomes between VATS SL and Open SL. The authors should clearly state in their introduction what makes the current study different, given the small sample size of their VATS SL group.

Reply: Thank you for this suggestion. We have added a line at the end of the paragraph where we mentioned the paper. We believe that our work adds support that PN and SL can be done using VATS.

Location: Introduction

Comment 6: Line 138-139: describes the aim of the study, however, the analysis and conclusion does not match this aim. The authors declare that they “aim to investigate if there exists a relationship between surgical approach and post-operative NSCLC patient outcomes” however, they report an analysis between SL and PN (Figure 1), in addition to their MVA investigating surgical approach.

Comment 7: Suggest performing comparative statistical tests to assess differences in stratified groups represented in Table 1

Reply: Thank you for this suggestion. We have edited our table one to alleviate ambiguity.

Location: Table 1

Comment 8: Reasons for return to OR in all patients. Was this due to bleeding?

Reply: Thank you for the question. Yes, bleeding was the reason in 6/11. 5 had had a BPF. We have added this to the manuscript.

Location: Results.

Comment 9: Suggest classifying complications using the clavien dindo method, rather than enumerating

Reply: Thank you for this suggestion. Due to the nature of our study the authors do not believe that analyzing complications in this manner would add merit to our results.

Comment 10: Table 4: suggest explicitly stating what the p value represents. Is it a difference in recurrence between PN and SL, or VATS/Open?

Reply: Thank you for this suggestion. We agree that this would add clarity and have edited the table.

Location: Table 4

Comment 11: Table 5: Reference level of each comparison is needed, as are confidence intervals. It appears that the p value of Open vs VATS is very close to significance, however, with such a low sample size, I am not sure that this is relevant at all.

Reply: Thank you for this comment. We have added confidence intervals to Table 5.

Location: Table 5

b) Minor Comments

Comment 1: I would recommend the authors use the same number of significant digits throughout the manuscript (p value, etc.).

Reply: Thank you for this suggestion. We agree that this would be more uniform and have changes the values.

Location: entire manuscript

Comment 2: Paragraph 130: suggest historical paragraph relating to VATS be moved earlier in introduction, or dismissed.

Reply: Thank you for this suggestion. We agree that because this is historical it does make more sense to have it sooner.

Location: it is now the first paragraph.

Comment 3: Line 138: suggest grammatical review

Reply: Thank you for the suggestion. We have revised the sentence.

Location: line 155

Comment 4: Line 145: spelling error: "Pateints"

Reply: Thank you for seeing this. We have fixed.

Location: line 163

Comment 5: Line 181: grammatical error, should read "There was no 30 day mortality"

Reply: Thank you for this edit. We have changed the results section and no longer have this phrase.

Location: Results

Comment 6: Line 181: grammatical error, missing 30 “day” mortality

Reply: Thank you for this edit. We have changed the results section and no longer have this phrase.

Location: Results

Comment 7: Line 190: spelling error: “Pateints”

Reply: Thank you for this edit. We have changed the results section and no longer have this phrase.

Location: Results

Comment 8: Line 218: the p values reported do not match those reported in table 5

Reply: Thank you for this edit. We have changed the values in the manuscript.

Location: line 243

Reviewer D

I would like to congratulate the authors for performing a very impactful study evaluating the outcomes of sleeve lobectomy vs pneumonectomy. I would also like to commend the authors for leading MIS approaches in lobectomy and pneumonectomy in the U.S.

Comments:

Abstract: I would shorten the introduction of the abstract

Reply: Thank you very much for this suggestion. The Introduction has been rewritten with this suggestion and those of the other reviewers in mind.

Location: Abstract

Results: I would recommend using the word "multivariable" instead of "multivariate"

Reply: Thank you very much for this suggestion we have changed the words.

Location: Results

Right now, I think a lot of the results are redundant with what is shown in the table. The results section can probably be abbreviated a bit.

Reply: Thank you for this comment. This message was shared by another reviewer as well. We have edited this section to be more abbreviated.

Location: Results

Table 3: I would recommend including the "%"

Reply: Thank you for the suggestion we had added them.

Location: Table 3

I would recommend thorough proofreading to fix the typos, grammar, and spelling errors.

Reply: Thank you very much for this suggestion. We have gone through the manuscript again to look for such errors.

Location: Entire Manuscript

Second-Round Peer Review

Reviewer B

The manuscript was a small study group and did not clearly indicate the inclusion criteria for PN and SL and the postoperative pathology status, which requested additional description.

Dear Reviewer B,

Thank you for reviewing our manuscript and aiding with the revision process. We have gone back into the manuscript in lines 164-167 and have attempted to elaborate further about the inclusion status. Due to the fact that this is a retrospective study we cannot be sure what the exact causes the surgeons had for choosing to perform a SL vs a PN. Because of this, we included all the patients that were operated on in this time period and included them in the study. The inclusion criteria was that the patients underwent surgery for oncologic reasons during the time period the study focused on. The post-operative pathology status was derived from looking at the pathology reports corresponding to the surgical samples sent during and after the surgical cases. The data can be found in Table 1.

Reviewer C

I thank the authors for providing insightful responses to my comments and including a series of changes in the manuscript, which I strongly believe has made the manuscript stronger.

However, I continue to take issue with the following major comments, which were not addressed to the standard that I believe the journal and its readership should expect. I assure you that the following comments are meant to strengthen your manuscript.

Dear Reviewer C,

Thank you for reviewing our manuscript and aiding with the revision process. We are grateful for your time and energy.

a) Major Comments

1. (Previous major comment 1) The authors should state whether they aimed to perform a non-inferiority analysis. Stating on lines 103-104 that VATS was found to be non-inferior to open surgical approach is misleading, as the study was not powered to detect non-inferiority. This is not a criticism of the sample size, it is a criticism of the conclusion drawn from the analysis.

Thank you for this comment and the clarification of the previous comment. We have clarified the wording and is still located on lines 103-104.

2. (Previous major comment 2) Given the retrospective nature of the analysis, patient factors can be obtained from the electronic medical record, such as PFTs (surely performed prior to sleeve lobectomy or pneumonectomy), ASA, or Zubrod Status. Without controlling for patient factors in the multivariate analysis, the positive 90d mortality result, for example, is extremely difficult to interpret. The authors must be well aware that close post-operative mortality is strongly associated with patient factors rather than oncologic factors. This must be accounted for in the analysis. Thank you for this comment. We agree that this data is important but when gathering data for this study all of the data were not able to be found leading to both the PN and SL groups being partially incomplete. Because this was a retrospective study, we cannot gain that data during the current time. We have elected to not include it rather than include incomplete data and risk incongruencies between the groups in respect to the missing data. We do not believe that the absence of the data significantly subtracted from our analysis.

3. (Previous major comment 4) I respectfully disagree with the authors that using a scale of days (to 5000 days) better illustrates the survival of patients included in this analysis. Should this manuscript have clinical implication, I fail to see how describing a median survival of 719 days compares to 1849 days to a patient with lung cancer would be clear at all (versus 24 months compared to 61 months). If the author state that there is a “greater change (...) when the data is analyzed using days” then we may have a statistical issue on our hands. Does the result of the analysis change when using a different format of the same exact metric?

Thank you for this comment. You are certainly correct with both comments that months will convey the information in a clearer manner and that the data remains the same when switching to a different format. We have made this change through the manuscript and we hope this will make it easier to interpret and less cumbersome on the reader. We have added a comment in our methods section (186-187) showing our conversion.

b) Minor Comments

Line 94: 90-day ($p=0.007$) should specify 90-day mortality, and p value should include the “0” in “.007” as well as throughout the paper.

We appreciate this comment and have changed the manuscript as per your suggestion.