Peer Review File

Reviewer A

First, we would like to congratulate the authors on their article entitled: "Outcomes following minimally invasive approaches vs open extended lobectomy for non small cell lung cancer a propensity matched analysis of the National Cancer Database". The article is well written and describes outcomes after open versus minimally invasive extended lobectomy in a large national cohort.

Please find our comments below per section.

Abstract

• It is generally known that lung cancer remains one of the most prevalent and deadly forms of cancer, you can leave this out of the manuscript.

Reply 1: Thanks for your comments. We will remove this sentence from the Abstract (see page 2, line 44-45).

Change in the text: see page 2, line 44-45

Introduction

• You outline the benefits of open versus MIS. Could you also elaborate on uniportal vs multiportal VATS vs. RATS on this topic?

Reply 2: Thank you for your advice regarding the detailed comparison of uniportal versus multiportal VATS versus RATS in minimally invasive extended lobectomy. Regrettably, there is a scarcity of literature on this subject, and our current database does not provide sufficient information about the number of ports used in surgeries. Consequently, we have decided not to include an extensive discussion on this in the Introduction section. We might consider writing a separate paper focused on this topic in the future.

Changes in the text: No.

• Please state the goal of your study more clearly. What is your primary outcome? What are secondary outcomes?

Reply 3: Thank you for highlighting the importance of clarifying our primary and secondary outcomes. Our primary outcome focused on the five-year overall survival rate following surgery. As for the secondary outcomes, they encompassed the safety and feasibility of the extended lobectomy. This included factors such as the length of hospital stay post-surgery, rates of unexpected readmissions within 30 days, and mortality rates at both 30- and 90-days post-surgery. We have added it in the text (see page 4, line 108-109).

Methods

• Why did you choose to do a 1:2 PSM, instead of 1:1 PSM?

• You state that the cutoff for inclusion was 2014 because of available results, however, for the short team results you could have included a lot more cases after 2014. Then you could also compare more cases that underwent RATS. Furthermore, long-term survival is a surrogate for oncological safety, which is also defined as R0 rate and number of resected lymph nodes. Since this is the same for open and MIS, the long-term survival can be expected to be the same as well.

Results

• It might be interesting to add pain scores or morphine equivalents for all groups if possible.

• What were the main reasons for conversion and did the conversion rate go down over the years? You do state this in your free text, however it does not appear to go down in figure 2. Again, interesting to include cases after 2014.

• Could you do subgroup analyses of the different types of extended resection? Complication rates or conversion rates could be different when comparing chest wall resection and pericardial resection for example.

Reply 8: Thank you for your suggestion regarding the potential for subgroup analyses on different types of extended resection. I appreciate the value such detailed analyses could bring. However, these specific analyses fall outside the central theme and objectives of the current article, which are focused on safety and feasibility of minimally invasive surgery for extended lobectomy and whether it can be adopted in the broader surgical community. While I agree that your proposed analyses could be interesting and clinically relevant, they would require a separate, dedicated study to be addressed appropriately. I will certainly keep your suggestion in mind for future research where it aligns more closely with the research objectives. For now, I must maintain the focus on the core findings that are most relevant to the theme of this article. Changes in the text: No.

Discussion

• Could you elaborate on why you think that more lymph nodes are harvested when comparted to open? And also why you believe LOS was shorter, and other results remained similar. In other words, why do you think the outcomes are the way they are?

Reply 9: Thanks for your comments. The increased lymph node harvest in minimally invasive surgery (MIS) may be due to the improved visualization and precision offered by this technique, allowing surgeons to identify and remove nodes more effectively. Additionally, surgeons performing VATS or RATS may have more experience and better surgical technique compared to those performing open surgery. The shorter length of stay (LOS) with MIS is typically attributed to patients experiencing less pain, quicker recovery, and fewer complications, which enables earlier discharge. The outcomes are a result of the proven advantages of MIS that have been demonstrated in numerous studies for early-stage lung cancer. For advanced-stage lung cancer, minimally invasive surgery may result in longer surgery time, but it can still provide non-inferior or even better perioperative outcomes.
Changes in the text: No.

Conclusion

• Might be important to mention that an experienced team is needed to adopt MIS for extended lobectomy.

Reply 10: Thank you for your reminder. We have added this in our text (see page 10, line 310). Changes in the text: page 10, line 310

Reviewer B

Thank you for this interesting paper.

1) I realize 5 year survival data is being used, but to me 2010 to 2014 is very old data especially with respect to MIS and open surgery, can you please have a cohort that is more recent perhaps include up to 2019? you should still be able to have plenty of time for 5 year data and if not, can you show 3 year OS data with newer dates?

Reply 1: Thank you for your suggestion. The data from 2010 to 2014 were the most recent available at the onset of our study that could provide a complete five-year survival analysis, which was crucial for our research objectives. Despite the older dataset, we believe our findings are valuable for understanding the trends and outcomes during that period, thus contributing to the historical context of MIS and open surgery techniques. Thank you again for your feedback. Changes in the text: No.

2) were you able to determine the preop mediastinal LN staging prior, meaning that should be a limitation that N stage was probably a biased factor?

Reply 2: Thanks for your comments. The preoperative mediastinal LN staging was determined by the imaging tests and biopsies of affected areas, but it was not accurate. We also believe that the clinical N stage may have been a biased factor, so we considered it as a potential bias factor in the propensity score matching (PSM) analysis. The results showed that after PSM, the clinical N stage was balanced between the minimally invasive surgery (MIS) and open surgery groups (refer to Table S1). Additionally, we conducted multivariable analyses to identify risk factors for overall survival in the entire study population. The results revealed that patients with clinical N2 stage exhibited worse survival outcomes compared to those with clinical N0 stage (refer to Table S3). We also presented the postoperative pathological N stage (refer to Table 1). Changes in the text: No.

3) Do you have data on how many patients had preoperative staging and biopsy of the primary prior to surgery? That can skew the results.

Reply 3: we apologized for not offering the numbers of patients having preoperative staging and biopsy of the primary prior to surgery. We do not currently have the data on preoperative staging and biopsy prior to surgery in our database. I apologize for any inconvenience this may cause.
Changes in the text: No.

4) The conclusion is nice, but again, probably overboard to say that MIS is the key and main factor for extended lobectomy given the high conversion rate?

Again it would be great to see a more recent cohort, since the majority of your MIS cohort was VERY small and indeed most were not RATS either, so even if you could show 1 and 3 year overall survival that would be nice with a more recent cohort?

5) How do the authors explain the higher rates of LNs in MIS for open surgeries, any thoughts?
Reply 5: Thanks for your comments. The increased lymph node harvest in minimally invasive surgery (MIS) may be due to the improved visualization and precision offered by this technique, allowing surgeons to identify and remove nodes more effectively. Additionally, surgeons performing VATS or RATS may have more experience and better surgical technique compared to those performing open surgery.
Changes in the text: No.

Reviewer C

This study addresses an intriguing topic through the use of a large-scale database, yielding several significant findings. However, the following issues can be identified:

Data Limitations and Interpretation Caveats:

Database Constraints: The study utilizes the NCDB, and due to the nature of the database, detailed information about specific patients or facilities may be lacking. Caution is required in interpreting the results and generalizing them, keeping this constraint in mind.
Reply 1: Thank you for your observation regarding the limitations of the NCDB data. We are aware that the granularity required for some analyses may not be present due to the anonymized and aggregate nature of the database. Despite this, we have taken utmost care in interpreting the results within these constraints, and we have emphasized the need for caution in generalizing findings. We are committed to ensuring the reliability and validity of our study findings within the scope of the data available.
Changes in the text: No.

Consideration of the Learning Curve:

High Conversion Rate in MIS: A high conversion rate in MIS extended lobectomy (28.3%) is

reported. The paper does not discuss how this conversion rate may be related to the learning curve or the experience of the operators. It is essential to explore whether the conversion rate decreases with improved operator experience.

Reply 2: We appreciate the comment pointing out the absence of discussion on the learning curve and operator experience in relation to the conversion rate in our study. We acknowledge that these factors could significantly influence the outcomes of MIS extended lobectomy. We briefly discussed the relationship between the conversion rate and learning curve (see page 8-9, line 254-268). The conversion rate was 35.3% in 2010 and 24.7% in 2014. Therefore, we believe that the conversion rate has decreased over the years (see Figure 2A).
Changes in the text: No.

Patient Population Selection Bias:

Use of PSM: The report employs propensity score matching (PSM), but it doesn't guarantee the equalization of patient populations. Patient selection biases or other unknown factors might still influence the outcomes.

Reply 3: Thank you for pointing out the limitations associated with the use of propensity score matching in our study. We recognize that while PSM is a powerful statistical technique for attempting to control for observable confounders and reduce selection bias in non-randomized studies, it does not account for unmeasured or unknown confounders. We have attempted to match the cohorts on a wide range of known variables to minimize potential biases.

In the discussion section, we have highlighted this limitation and have been careful not to overstate our findings. Nevertheless, we agree that the potential influence of unobserved variables remains a valid concern. We advocate for caution in interpreting our results and acknowledge the need for further studies, including randomized trials where possible, to confirm our findings.
Changes in the text: No.

Details of Statistical Analysis:

Survival Analysis: In survival analysis, more detailed statistical methods and explanations for variable selection are needed. Although a Cox proportional hazard model is used, information regarding the model selection process and criteria for variable inclusion is lacking.

Reply 4: We appreciate the reviewer for pointing out the need for a more detailed explanation of our statistical methods and variable selection process in the survival analysis. In response to this feedback, we will update our manuscript to provide a more comprehensive description of our approach to model selection for the Cox proportional hazards model (see page 5, line 159-160). For the Cox proportional hazards model, we selected demographic and

clinicopathological characteristics, as well as surgical information, as our variables. We would like to emphasize that our use of the Cox proportional hazards model aims to demonstrate that the surgical approach (either minimally invasive or open) is not a risk factor for overall survival in the entire study group.

Changes in the text: page 5, line 159-160.

Lack of Important Parameters such as Operative Time:

Reporting Operative Time: There is insufficient comparison of operative time between MIS and open surgery. If the operative time for MIS is longer than that for open surgery, the impact and benefits need to be considered.

While considering these issues, the results of the paper should be examined. Particularly, future research should focus on these concerns, conducting more detailed analyses and providing comprehensive information.

Reply 5: Thank you for the insightful comments regarding the comparison of operative times between minimally invasive surgery (MIS) and open surgery. Due to the limitations of the National Cancer Database (NCDB), we did not have access to the specific operative time data in our study. We have acknowledged this as a limitation and discussed it in our paper (see page 10, line 299). Based on our experiences, we have found that extended lobectomy performed via MIS generally takes longer operative time compared to thoracotomy. However, we still believe that it is worth considering MIS as the first approach due to its potential benefits such as reduced pain, fewer complications, better recovery, and shorter length of post-operative stay.

Changes in the text: No.

Reviewer D

The authors analyzed the safety, feasibility, and efficacy of minimally invasive extended lobectomy (defined as lobectomy or bilobectomy with chest wall, diaphragm or pericardial resection) in patients diagnosed with NSCLC. They found that the reduced average postoperative hospital stay for the MIS group at 7.15 days compared to the open group at 8.40 days (P<0.001). Furthermore, the 5-year survival rate was similar, with the MIS group at 53.1% and the open group at 51.3% (P=0.683). They suggested that MIS for extended lobectomy not only is safe and feasible but also is oncologically effective.

I have the following concerns.

Comment 1

Introduction

The authors aimed to clarify the safety, feasibility, and efficacy of minimally invasive extended lobectomy in patients diagnosed with NSCLC. Please state the c of the study in the Introduction.

Reply 1: Thank you for highlighting the importance of clarifying our purpose. Our primary outcome focused on the five-year overall survival rate following surgery. As for the secondary outcomes, they encompassed the safety and feasibility of the extended lobectomy. This included factors such as the length of hospital stay post-surgery, rates of unexpected readmissions within 30 days, and mortality rates at both 30- and 90-days post-surgery. We have added it in the text (see page 4, line 108-109).

Changes in the text: page 4, line 108-109

Comment 2

Statistical analysis

A more detailed description of the PSM methodology is needed. Example statements are represented below.

Ex) Propensity scores were estimated using a logistic regression model. The two groups were matched in a 1:2 ratio, with a standard deviation of less than 0.20 logit of the propensity score.

Reply 2: Thank you for the feedback regarding the necessity of providing a more detailed description of our propensity score matching (PSM) methodology. We have added this in the text (see page 5, line 152-156).

Changes in the text: page 5, line 152-156.

Comment 3

To check if the populations are comparable after PSM, p-values are not a good tool and standardized differences should be used instead.

Reply 3: Thank you for your suggestion to use standardized differences to evaluate comparability between populations after PSM. While I acknowledge the value of standardized differences in certain contexts, for this particular analysis, we have opted to use p-values.

Changes in the text: No.

Comment 4

In this study, surgery was performed on patients with predominantly clinical T1,2 and clinical N0. In general, standard lobectomy is sufficient for most of these patients.

Again, this study analyzes the results of extended lobectomy. Therefore, the authors need to indicate what extended lobectomy has become necessary. The current tables show results for NOS and 46-48. Detailed data on 46-48 are important results. Please supplement the results and tables with more details on expanded lobectomy.

Reply 4: Thank you for your valuable feedback. We agree that standard lobectomy is often sufficient for patients with clinical stage T1 or T2 and N0, and the necessity for extended

lobectomy in our study requires clearer justification. Unfortunately, this is not stated clearly in the NCDB. In our experience, if the tumor is adhered to the chest wall, diaphragm, or pericardium, extended lobectomy is usually needed to ensure negative margins. However, adhesion does not necessarily indicate tumor invasion. Pathological examination is needed to confirm this. The number of patients with code 46-48 was 189 (27.5%) in the MIS group and 1138 (38.2%) in the open group.
Changes in the text: No.

Comment 5

This paper provides a statistical analysis of postoperative outcomes that includes several subgroups. The authors should add more details about the analyses performed in the Methods section.

Reply 5: Thank you for your valuable feedback regarding the statistical analysis section in our paper. We have added this in our paper (see page 5-6, line 163-164).
Changes in the text: page 5-6, line 163-164

Comment 6

In Comparison of the MIS and open groups in the community/comprehensive hospital setting, the R0 rates were higher in the MIS group after PSM (90.2% vs. 85.5%, P=0.047).
However, there was no significant difference in overall survival between the two groups after PSM. Although postoperative results compare positive metastatic lymph nodes, I recommend comparing the pathological stage. Was there a statistical difference in pathological stage in each group analysis?

Reply 6: Thanks for your valuable feedback on the comparison of the pathological stage. Table 1 presents the surgical outcomes in terms of the pathological stage. The comparison reveals a statistically significant difference in the pathological T stage between the two groups. The MIS group had a higher proportion of early-stage lung cancer, whereas the open group had a higher proportion of advanced-stage lung cancer. However, there was no statistically significant difference in the pathological N stage.
Changes in the text: No.

Comment 7

According to Table 1, the pathological stages are T1,2 in 60% and N0 in 70%. Furthermore, pT3 or higher is 30% and pN2 is less than 10%.
More advanced patients are not included in greater numbers than expected, especially in the T factor. Readers may distrust the study data because the study included patients who required Extended Lobectomy. Detailed results of Extended Lobectomy need to be clarified to prove the reliability of the data.

Reply 7: We apologize for not offering the detailed results of extended lobectomy. The NCDB

database doesn't contain detailed records of extended lobectomy procedures; therefore, we're unable to provide the requested specifics.
Changes in the text: No.

Comment 8

For Extended Lobectomy, the main topic of this paper, MIS had no prognostic impact.

In terms of perioperative mortality, MIS was comparable to Open. On the other hand, MIS showed a high open conversion rate, making it questionable whether MIS can be recommended as a safe approach.

In my opinion, the conclusions of this paper are as follows: MIS had a similar prognosis to Open. MIS Extended lobectomy had a high open conversion rate, but is effective in shortening LOS if not converted to open surgery.

Additionally, I recommend adding the following comments to the text.

Perioperative management for open conversion is essential if extended lobectomy is anticipated preoperatively. In addition, a surgical team skilled in MIS should be assembled because it will be a challenging procedure.

Reply 8: Thank you for your insightful observations. We will incorporate the recommended comments on perioperative management and the importance of an experienced MIS surgical team for challenging procedures (see page 10, line 316-320). Your suggestions are greatly appreciated and will certainly enhance the manuscript.

Changes in the text: page 10, line 316-320

Comment 9

Please add the main reason for conversion from MIS to open surgery.

Reply 9: We apologize for not mentioning the reason for the conversion. The reason for the conversion was not available in the NCDB. Based on our experience, calcified lymph nodes and unexpected bleeding are the main reasons for converting to open surgery during minimally invasive surgery (MIS).

Changes in the text: No.

Comment 10

Fig3D shows a comparison between Open and Conversion.

MIS and Open are correct?

Reply 10: Thanks for pointing out our mistake in Fig 3D. we have made it correct.

Changes in the text: page 17, Fig 3D.

Comment 11

The titles of some tables are perioperative results. Since only postoperative results are shown,

please change to appropriate titles such as postoperative results or surgical results.

Comment 12

Please use the same font in the text.

This is an interesting consideration, but the study has significant issues.

The study focuses on extensive lung lobe resection involving the chest wall, diaphragm, and pericardium, yet it includes many cases with cT2 or lower.

While this is mentioned in the limitation section, not understanding the underlying reasons poses a significant threat to the overall reliability of the database.

This is a scientific paper. Publishing the current content is not acceptable, and there are strong doubts about the reliability of the database.

If the goal is to pursue publication for this research, it is necessary to narrow the scope to include only cases with cT3,4 and pT3,4.

In this manuscript the Authors report the results of a study designed to compare the outcomes of open and minimally-invasive surgery (MIS) for extended lobectomy in patients with non-small cell lung cancer recruited among the National Cancer Database. After propensity-score matching, 683 minimally-invasive and 1.317 open-surgery patients were included in the analysis. The results of the study show that with MIS postoperative hospital stay was significantly shorter and the number of dissected lymph nodes was higher, with an equivalent

5-year overall survival. Complete resection rates and 30 and 90-day mortality were similar in the two study groups. Similar results were also observed with VATS and RATS approaches. After conversion to open surgery, reported in about 28% of the patients, the outcome was not worse than after upfront open surgery. A trend towards better results with MIS in the last years of the study was observed, likely to the progression of the learning curve. The manuscript may be of interest, despite some limitations as the lack of information concerning tumor recurrence. However, the main issue concerns the fact that most of the procedures included in the analysis were not classified according to the type of complex lobectomy. This point, despite the use of propensity-score matching, may have influenced the results of the study. In fact, a selection bias may be present, with more complex procedures and more advanced tumors approached by open surgery. This point should be commented by the Authors.

Reply 1: Thanks for your comments. The number of patients with code 46-48 was 189 (27.5%) in the MIS group and 1138 (38.2%) in the open group (see Table S1). As a retrospective study, it is hard to avoid selection bias completely. We used PSM to balance the demographic and clinicopathological characteristics. Whether choose MIS or not depends on surgeons' judgement and experiences. We concluded that extended lobectomy via MIS could be attempted first by experienced surgical teams.
Changes in the text: No.