Peer Review File

<mark>Reviewer A</mark>

1. The title is not very clear, for example, comparing SV-VATS with MV-VATS. The second issue is the lack of safety outcomes in the title and abstract. In general, efficacy and safety are equally important in clinical trials.

Reply: Thank you for the advice. We agree that the title and abstract were incomplete, because of the lack of safety outcomes.

Changes in the text:

Line 1-2 Perioperative and Long-term Outcomes of Spontaneous Ventilation Video-assisted Thoracoscopic Surgery for Non-Small-Cell Lung Cancer

Line 50-53 There were no statistically differences between SV-VATS and MV-VATS in the operative time (158.56 ± 40.09 vs. 172.06 ± 61.75, p=0.200) anesthesia time (247.4 ± 62.49 vs. 256.7 ± 58.52, p=0.528), and intraoperative bleeding volume (78.88 ± 80.25 vs. 109.932 ± 180.86, p=0.092).

2. English language of the paper needs further editing, i.e., "before analyzation" and "For two group analysis". Please do not use Chinese-English sentences.

Reply: Thank you for the suggestion. We altered the sentences in the article.

Changes in the text: Please check in manuscript.

3. Abstract. In the background part, it remains unclear the clinical significance of comparisons between SV-VATS and MV-VATS. In the part of methods, please use PICOS criteria to describe the inclusion of eligible NSCLC patients. The authors need to briefly describe the assessment of outcomes, for example, how these patients were followed up.

Reply: Thank you for the suggestion. We added details in the abstract, please check.

Changes in the text:

Line 28-32: Spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS) exhibits dual intraoperative and postoperative advantages for patients with non-small-cell lung cancer (NSCLC). However, there is a lack of data regarding its long-term survival superiority over the double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery (MV-VATS) or thoracotomy.

Line 35-44: Patients receiving the SV-VATS were the experimental group, and patients receiving the MV-VATS were the control group. Propensity score matching (PSM) was performed to establish 1:1 SV-VATS versus MV-VATS group matching to balance potential baseline confounding factors. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Secondary endpoints were perioperative outcomes. The baseline information of these patients was recorded. The perioperative data and survival data were collected using a combination of electronic data record system and telephone interview. A 1:1:1 SPM was

also used to compare the OS in the SV-VATS, the MV-VATS and thoracotomy group by using another database, including patients undergoing thoracotomy and the MV-VATS.

4. Although PSM resulted in comparable SV-VATS and MV-VATS groups, the majority of patients receiving MV-VATS were not included in the analysis, which is a significant resource of selection bias in the sample of patients receiving MV-VATS. The authors must make their conclusion with cautions and discuss this limitation in the part of discussion. I also suggest the authors to compare the results with and without PSM to see whether the current findings are stable, which is sensitivity analysis.

Reply: Thank you for your advice. Since the TNM stage of the MV-VATS group before PSM was higher than the SV-VATS group after PSM, it was assumed that the long-term survival outcomes of the MV-VATS before PSM was also worse than the SV-VATS group after PSM. Therefore, we regarded the sensitivity analysis is not necessary. The limitation of PSM was stated in the part of discussion.

Changes in the text:

Line 328-331: First, there may have been selection bias despite the use of 1:1 or 1:1:1 PSM, as patients were not randomized before the surgery and the majority of patients undergoing MV-VATS or thoracotomy were excluded after PSM in our analysis.

5. Introduction. A brief review of the long-term outcomes of MV-VATS is needed in this part, including safety outcomes. Although long-term evidence of the outcomes of SV-VATS is lacking, the authors may consider to have some speculations based on the short outcomes or theoretical speculations. This could provide some bases for the current comparisons. In the main text, the authors also compared SV-VATS with thoracotomy, but in this part, they only mentioned MV-VATS. If the comparison groups were the two, the authors should also have a brief review on thoracotomy in this part.

Reply: Thanks for your suggestion. We added details in introduction, please check.

Changes in the text:

Line 68-70: Before the widely use of video-assisted thoracoscopic surgery (VATS) in 1990s, thoracotomy was the only option in thoracic surgery (2, 3).

Line 70-74: The past decades have witnessed the gradual replacement of thoracotomy by double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery (MV-VATS) for its better short-term postoperative outcomes, including less incidence of complications (4, 5). The long-term survival outcomes of patients underwent lobectomy by MV-VATS were no inferior to thoracotomy (6).

Line 87-95: Though the intraoperative and postoperative advantages of SV-VATS over MV-VATS have been indicated, there is a lack of study reported its long-term benefit for patients with non-small-cell lung cancer. Because of the relatively unstable operation field and moving of mediastinal structures, some researchers may question whether the systematic lymph node dissection under the SV-VATS is eligible and long-term outcomes compared to MV-VATS (11). It was hypothesized that the long-term outcomes of the SV-VATS was not inferior to or

even better than the MV-VATS according to the better perioperative outcomes, with less opioid use and less inflammatory response (18, 19).

6. Methodology. At the beginning of this part, please clearly indicate the clinical research design of this study, i.e., a cohort or prognosis study. In this part, patients decided whether they received SV-VATS or MV-VATS. This may be difficult for patients, and it seems unusual that no involvement of surgery physicians in the clinical decision-making for the treatment choice of patients. Please revise the current sentences to make them accurately and clearly.
Reply: Thank you for the advice. This study was a retrospective analysis. Besides, we are sorry for not clearly stated in the paper. The thoracic surgeons and anesthetists evaluated all patients before operation. After fully explanation and description of the difference between the SV-VATS and MV-VATS during preoperative publicizing and education by surgeons, all patients were asked whether they would like to receive the SV-VATS. Patients who disagreed would be given the MV-VATS. Anesthetists would visit each patient to determine who may receive this new technique.
Changes in the text: Line 122-125: An informed consent for the SV-VATS or the MV-VATS group was obtained from all the patients including explanation of the reason, modalities, risks and benefits. The decision of the surgical type was made by thoracic surgeons, anesthetists and patients together before operation.

7. Statistics. Please specify P<0.05 is two-sided or not. As I comment above, PSM also has limitations, the authors may consider to have an extensive discussion on this or do sensitivity analysis. The authors need to further clarify the sentence "Patients who were lost during follow-up were censored in the survival analysis." Does this mean these patients were excluded from the analysis?
Reply: Thank you for the question. We added the details in the part of methods. The limitation was added in the part of discussion. Patients who were lost during the follow-up and patients were alive until July 2021 were set as censored in the Kaplan-Meier method and the log-rank test, instead of removing.
Changes in the text:
Line 164-166: For patients who lost to follow-up, they were evaluated by the latest medical record or telephone interview.
Line 198-199: All statistical tests would be performed two-sided with a level of significance of 5%.

This manuscript describes the Long-term outcomes of spontaneous ventilation video-assisted thoracoscopic surgery(SV-VATS) for non-small cell cancer. This author suggests the prognostic advantage of SV-VATS lobectomy for invasive non-small cell lung cancer patients compared to mechanical ventilation VATS(MV-VATS) and open thoracotomy. The new

aspects that SV-VATS had prognostic benefits because of the reduction in the prescription of postoperative opioids, the usage of the regional anesthesia and propofol-TIVA (total intravenous anesthesia) are presented. However, data in this manuscript is not based on scientific basis.

Major visions are shown as below.

1. The results of this retrospective study are derived from single institute and relevant scientific evidence is insufficient. Especially, P value is 0.0498 on the basis of the comparative study between SV-VATS and MV-VATS as for the overall OS rate. To conduct a multicenter prospective observational study may be desirable.
Reply: Thanks for your advice. Since we conducted a single center study instead of multicenter prospective observational study, the evidence was insufficient for the conclusion in this study. Multicenter prospective observational studies need to be conducted to confirm the survival advantages in the SV-VATS.
Changes in the text: Line 337-338: Further RCT studies and multicenter prospective observational studies need to be developed to confirm the survival advantages in the SV-VATS.
2. As for the beneficial effect of SV-VATS, if the author monitors the inflammatory markers such as cytokines related to oncological environments, the results of this data may increase the reliability.
Reply: Thanks for your advice. The inflammatory markers such as cytokines may also explain the beneficial effect of SV-VATS. Unfortunately, we didn't collect and couldn't analyze these data in our study.
Changes in the text: Because of the insufficient data, we couldn't analyze the data of inflammatory markers in our study, so there is no change in the study.
3. There was no data of the consumption of opioids and TIVA of SV-VATS, MV-VATS and open thoracotomy in this manuscript. The author should show relevant data.
Reply: Thanks for your question and suggestion. We didn't record the concrete consumption of opioids and TIVA in this retrospective study. The specific data and information can be found in the previous RCT study in our center (Liu J, Liang H, Cui F, Liu H, Zhu C, Liang W, et al. Spontaneous versus mechanical ventilation during video-assisted thoracoscopic surgery for spontaneous pneumothorax: A randomized trial. J Thorac Cardiovasc Surg. 2021.).
Changes in the text: Line 132-133: All procedures and consumption of anesthesia were described in the previous study (18, 20, 21).

<mark>Reviewer C</mark>

First, please justify the absence of the registration of the trial. The ethical issues should be better discussed.

Reply: Thanks for your question. This study was reviewed by the institutional ethics committee of the First Affiliated Hospital of Guangzhou Medical University (2020-69). And it was absent of the registration of the trial for it was a retrospective study.

Changes in the text: There were no change in the text.

The statistical analysis should be written according to the recently published guidelines (Hickey GL, Dunning J, Seifert B, Sodeck G, Carr MJ, Beyersdorf F on behalf of the EJCTS and ICVTS Editorial Committees Editor's Choice: Statistical and data reporting guidelines for the European Journal of Cardio-Thoracic Surgery and the Interactive CardioVascular and Thoracic Surgery. Eur J Cardiothorac Surg 2015;48:180-93).

Reply: Thanks for your suggestion. We improved the writing of statistical analysis in the Methods and Results.

Changes in the text: Please check in the text.

The limitations section should be improved with a better discussion.

Reply: Thanks for your suggestion. We improved the limitations section with a better discussion.

Changes in the text: Line 328-338: There are some limitations in our study. First, there may have been selection bias despite the use of 1:1 or 1:1:1 PSM, as patients were not randomized before the surgery and the majority of patients undergoing MV-VATS or thoracotomy were excluded after PSM in our analysis. Second, as the technique of the SV-VATS was not mature at the beginning of application, the difference in experience of surgeons may bring potential bias. Third, the sample size was not large enough. There were 400 patients included after PSM in this retrospective analysis. Besides, the follow-up time was not long enough. Though we followed up two groups of patients for more than 4 years on average, the follow-up time was not long enough to calculate the median survival time of SV-VATS. Further RCT studies and multicenter prospective observational studies need to be developed to confirm the survival advantages in the SV-VATS.

Besides, the discussion should be improved with a better search of the literature.

Reply: Thanks for your suggestion. We improved the discussion with a better search of the literature.

Changes: Please check in the text.

About minor points, there are grammars and typos errors in the text. Please thoroughly check the article.

Reply: Thanks for your advice. We checked the article and correct the grammars in the text.

Changes in the text: Please check in the text.

Good luck with your article, and thanks again for submitting it.

Reviewer D

I would like to congratulate the authors for conducting this very important and interesting study. Despite the mentioned limitations, this study is the first to investigate the survival

aspect following SV-VATS. The results of the study are very valuable and encouraging. Use of PSM was very important to eliminate the bias. SV-VATS is surely one of the most important cornerstones of thoracic surgery in the modern era.

I had a few suggestions (s. attachment) and minor comments. Despite some typos, the manuscript has a clear structure and is well-written. I congratulate the authors again for their effort.

Line 57: invasive NSCLC patients underwent SV-VATS lobectomy were associated with better → invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 57-58: Conclusion Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

Line 118: it would be better to replace the phrase "experimental group" by "study group" in this line as well as all the following lines, where it is mentioned
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Please check in the text.

Line 120: The criteria of recruiting patients under the SV-VATS, the criteria were as follows → The criteria of recruiting patients under the SV-VATS were as follows
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 127: The criteria of recruiting patients under the SV-VATS were as follows:

Line 125: all anesthesia process was desbribed → all anesthesiologic procedures were described
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 132-133: All procedures and consumption of anesthesia were described in the previous study (18, 20, 21).

Line 134 and intercostal nerve block, was managed → were applied
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 140-142: Moreover, regional block anesthesia, including local anesthesia at the incision, thoracic vagus nerve block, pleural surface block, and intercostal nerve block, were applied (20).

Line 138 were routinely tested and continually tested and monitored → were routinely measured and continually monitored

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 144-147: Perioperatively, end-tidal carbon dioxide partial pressure, pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG), and noninvasive blood pressure were routinely measured and continuously monitored both in the SV-VATS group and the MV-VATS.

Line 143 the same in different anesthesia methods → the same in both anesthesia methods

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 150-151: The standard NSCLC radical surgery progress, including lobectomy and lymph node dissection, was the same in both anesthesia methods.

Line 143 uniportol or double portol → uniportal or biportal

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 151-152: Uniportal or biportal VATS was adopted.

Line 172 data are given as mean → data are shown as mean

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 189-190: Continuous data were shown as mean ± standard deviation (SD), and categoric data were displayed as a count and percentage of patients.

Line 174 taken to → applied to

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: ine 190-192: Fisher's exact test was applied to compare the difference of continuous data, while the student's t-test was used in categorize variables.

Line 175 to caterorize variable → in categoric variables

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 190-192: Fisher's exact test was applied to compare the difference of continuous data, while the student's t-test was used in categorize variables.

Line 176 Univariable and multivariate → univariate and multivariate

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 193-194: Univariate and multivariate Cox regression analysis was conducted to assess the potential factors affecting survival.

Line 183 we analyze → we analyzed
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 201-202: In order to further explore the long-term benefit of the SV-VATS, we compared the OS of patients with NSCLC who underwent SV-VATS, MV-VATS and thoracotomy.

Line 184 undertook → underwent
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 201-202: In order to further explore the long-term benefit of the SV-VATS, we compared the OS of patients with NSCLC who underwent SV-VATS, MV-VATS and thoracotomy.

Line 185 undertook → underwent
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 203-204: A database (database 2) including patients undergoing thoracotomy and MV-VATS from multi-institutions in China between 2001 and 2008 was used in this study (6).

Line 197 were displayed → are displayed
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Change in the text: Line 215-217: 400 (200: 200) patients remained after the PSM. Features and baseline information of all patients before and after 1:1 PSM are displayed in Table 1.

Lines 200 and 201 No patients in SV-VATS group were transferred → None of the patients in the SV-VATS group required conversion to the MV-VATS methods
Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 219-220: None of the patients in the SV-VATS group required conversion to the MV-VATS methods.

Lines 203 and 204 of the SV-VATS group → of the SV-VATS group and MV-VATS group did not show significant differences. Moreover, no significant differences regarding the intraoperative bleeding volume were observed between the two groups.
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language.

We corrected the sentence.

Changes in the text: Line 221-224: There were no statistical differences between two groups (SV-VATS versus MV-VATS) in the operative time (158.56 ± 40.09 vs. 172.06 ± 61.75, p=0.200) anesthesia time (247.4 ± 62.49 vs. 256.7 ± 58.52, p=0.528), and intraoperative bleeding volume (78.88 ± 80.25 vs. 109.932 ± 180.86, p=0.092).

Line 212 were shown → are shown

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 230-231: Other preoperative, intraoperative, and postoperative outcomes were similar in two groups (Table 2).

Line 216 Rate of 3-year and 5-year → Rates of 3-year and 5 -year

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 236-240: In the SV-VATS group, 3-year and 5-year OS rates were 95.0% (91.9%-98.1%) and 90.8% (86.1%-95.5%), and 3-year, 5-year DFS rates were 90.5% (86.2%-94.8%) and 85.5% (79.4%-91.6%), respectively. In the MV-VATS group, 3-year, and 5-year OS rate were 87.3% (82.6%-92.0%) and 82.7% (77.2%-88.2%), and 3-year, 5-year DFS rate were 80.8% (75.3%-86.3%) and 76.3% (70.2%-82.4%) for NSCLC patients.

Line 223 which shown in → which is shown in

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 240-243: The SV-VATS group was associated better OS (HR=0.567, 95% CI 0.330 to 0.974, p=0.0498) and DFS (HR=0.546, 95% CI 0.346 to 0.863, p=0.013) than the MV-VATS group (Figure 2).

Line 225 including the status of anesthesia methods → including the mode of anesthesia

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 247-250: Variables, including the mode of anesthesia methods (p=0.015), T stage (p<0.001), N stage (p<0.001), and TNM stage (p<0.001) were significant prognostic factors for DFS by univariate Cox analysis, and T stage (p<0.001), and N stage (p<0.001) were significant prognostic factors for OS.

Line 227 and status of gender → and gender

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 247-250: Variables, including the mode of anesthesia methods (p=0.015), T stage (p<0.001), N stage (p<0.001), and TNM stage (p<0.001) were significant

prognostic factors for DFS by univariate Cox analysis, and T stage (p<0.001), and N stage (p<0.001) were significant prognostic factors for OS.

Line 229 that status of anesthesia methods → that mode of anesthesia
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 247-250: Variables, including the mode of anesthesia methods (p=0.015), T stage (p<0.001), N stage (p<0.001), and TNM stage (p<0.001) were significant prognostic factors for DFS by univariate Cox analysis, and T stage (p<0.001), and N stage (p<0.001) were significant prognostic factors for OS.

Line 231 and status of anesthesia → and mode of anesthesia
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 250-253: Additional multivariate analysis indicated that mode of anesthesia methods (p=0.001), and T stage (p=0.015) were independent factors for DFS, and mode of anesthesia methods (p=0.004), and T stage (p=0.037), were independent factors for OS (Table3).

Line 234 among three group → among three groups
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 254: Comparison among three groups (SV-VATS, MV-VATS, Thoracotomy)

Line 249 that explores → that proves
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 270-271: This is a study that retrospectively proves the survival superiority of patients underwent the SV-VATS lobectomy and lymph node dissection over the MV-VATS.

Line 254 include without tracheal intubation → include absence of endotracheal intubation
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 275-277: Previously, the characters of the non-intubated SV-VATS, included absence of endotracheal intubation and muscle relaxants during anesthesia induction, intravenous sedative, and less intravenous analgesics and opioids (20, 21).

Line 256 which reported → which was reported
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language.

We corrected the sentence.

Changes in the text: Line 275-277: Previously, the characters of the non-intubated SV-VATS, included absence of endotracheal intubation and muscle relaxants during anesthesia induction, intravenous sedative, and less intravenous analgesics and opioids (20, 21).

Line 258 → reduced hospital stay → reduced length of hospital stay

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 277-278: The SV-VATS was associated with a faster postoperative recovery, decreased complications, and reduced length of hospital stay.

Line 261 was the sharply reduction → was the sharp reduction

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 285-287: One of the most essential characteristics of the SV-VATS compared to the MV-VATS was the sharp reduction of opioid analgesics, which might accelerate recurrence of cancer.

Line 262 vitro studies → in-vitro studies

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 287-289: In vitro studies, it have been proved that opioids possess the pro-tumor activity and leads to tumor progression through immunosuppression, angiogenesis, and migration of tumor cells (29).

Line 273 was thoroughly used → was thorough use of regional anesthesia

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 298-299: Another characteristic of the SV-VATS compared to the MV-VATS was full utilization of regional anesthesia (20, 21).

Line 275 for operable oncology patients → for operable oncological patients

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 299-301: A meta-analysis indicated that epidural anesthesia and analgesia might be related to the increased OS for operable oncological patients (36, 37).

Line 278 oncology patients → oncological patients

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 303-304: The regional anesthesia may influence the survival outcome of oncological patients by suppressing immune defense mechanisms in the perioperative period (38).

Line 280 had contrast → had controversial results
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 304-306: However, there are no consensus on the association between regional anesthesia and survival outcome in oncological patients.

Line 281 oncology patients → oncological patients
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 304-306: However, there are no consensus on the association between regional anesthesia and survival outcome in oncological patients.

Line 281 manifested → demonstrated
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 306-308: The analysis of a randomized controlled trial (RCT) demonstrated that regional anesthesia did not associate with lower recurrence of breast cancer after surgery (39).

Line 282 associate with lower the breast → with lower recurrence of breast cancer after surgery
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 306-308: The analysis of a randomized controlled trial (RCT) demonstrated that regional anesthesia did not associate with lower recurrence of breast cancer after surgery (39).

Line 283 illustrated the negative result → showed the negative result
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 308-310: Another RCT by Paul S. et al. (40), showed the negative result of the relationship between epidural analgesia and the intravenous analgesia in surgery for patients with abdominal cancers.

Line 289 about the vitro results → about the in-vitro results
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 313-315: There were several in-vitro studies showed a pro-metastatic impact of volatile anesthesia and an antimetastatic impact of intravenous anesthesia (42, 43).

Line 297 contrast result → contrary result
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 320-322: In patients with digestive tract surgery, an observational study demonstrated a contrary result that there was no difference in OS and RFS between volatile and intravenous anesthesia (46).

Line 303 in spite → despite the use
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 328-331: First, there may have been selection bias despite the use of 1:1 or 1:1:1 PSM, as patients were not randomized before the surgery and the majority of patients undergoing MV-VATS or thoracotomy were excluded after PSM in our analysis.

Lines 317 and 318 underwent → undergoing SV-VATS lobectomy show better long-term
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 341-342: Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

<mark>Reviewer E</mark>

This is manuscript from Professor He's group, studied the long-term outcome of Spontaneous Ventilation Video-assisted Thoracoscopic Surgery (SV-VATS) for Non-Small-Cell Lung Cancer, in comparison with a retrospective cohort of cases performed under VATS or thoracotomy using mechanical ventilation (MV). Professor He's group is one of the leaders in the field of VATS and spontaneous ventilation technique, and this topic is of interest to the wider audience of thoracic surgery.

Using propensity score matching(PSM), the authors had reported that the disease free survival(DFS) and overall survival(OS) was better in the SV-VATS group. Hence, they have concluded that invasive NSCLC patients undergoing SV-VATS lobectomy were associated with better long-term outcomes compared with MV-VATS and thoracotomy.

While the manuscript is worthy of publication, there are several concerns in which the authors will need to clarify:

1. From the description as well as previous publication from Professor He's group (doi:10.1093/ejcts/ezw160), SV-VATS were used for lobectomy around late 2011. However, the curent comparison group included patients that pre-dated the introduction of SV-VATS. It is well-documented that survival for lung cancer has been consistently improving over the past few decades due to concurrent improvement in diagnosis and treatment. The inclusion of mechanical ventilated patients pre-dating the start of SV-VATS therefore introduced the confounding effects of diagnostic and treatment improvement that is not adjusted for by PSM. To make a more convincing comparison between SV and MV VATS, the authors will need to consider using MV VATS cases only from 2011 to avoid such bias. Even then, it may be difficult to show that it is superior as there will be always intrinsic selection bias that cannot be eliminated, such as why certain patients were not suitable for SV VATS and only suitable for MV VATS.

Reply: Thanks for your question. We agree your opinion and re-analyzed data in this study. The data was reviewed and patients who underwent operation before 2011 were excluded. PSM, Chi-2 test or Fisher's exact test and student's t-test for baseline information, the Kaplan-Meier method and the log-rank test for survival outcomes, and Cox were all reanalyzed. It was found out that the SV-VATS group was associated better OS (HR=0.567, 95% CI 0.330 to 0.974, p=0.0498) and DFS (HR=0.546, 95% CI 0.346 to 0.863, p=0.013) than the MV-VATS group (Figure 2).

Changes in the text: Please check in the text and Figure 1.

2. For the above reasons stated in point 1, the use of multi-institutional datasets for MV VATS and thoracotomy from 2001-2008 also does not provide convincing evidence that the survival benefit observed is due to SV-VATS. It is possible that survival benefit observed may be partly due to improvement in cancer management in the new decade as well. There were also further confounding factors not accounted for by PSM such as variations in anaesthetic and surgical outcome within different institutions. Therefore, there may not be much merit in using this dataset for such analysis. It may be possible use this dataset to state that SV-VATS provide comparable results to historical data performed using VATS and thoracotomy with MV, however, it will be necessary to interpret this results with caution in the context of the confounding factors outlined above.

Reply: Thanks for your suggestion. This study mainly demonstrated the better survival long-term outcomes of SV-VATS compared to MV-VATS. And the comparison among group SV-VATS, MV-VATS and thoracotomy was supplement for the beneficial survival outcomes of SV-VATS.

Changes in the text: Line 57: Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

3. With regards to the use of multi-institutional datasets, the authors will also need to clarify whether there were ethical approvals from the respective institutions specifically for its use for this study? If not, it may be best not included such analysis.

Reply: Thanks for your suggestion. The ethical approvals were obtained from the respective

institutions specifically, which had been included in our previous study (Cao C, Zhu Z-H, Yan TD, Wang Q, Jiang G, Liu L, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small-cell lung cancer: a propensity score analysis based on a multi-institutional registry. Eur J Cardiothorac Surg. 2013;44(5):849-54).

Changes in the text: Line 205: Ethics approval was obtained from eight institutions.

4. 20% of patients have nodal involvement after PSM from both groups – did these patients received and complete adjuvant therapy? This data should be included. It is not also very clear in the manuscript whether this is factor in the analysis as this will affect the overall survival and DSF.

Reply: Thanks for your question. All patients of stage ⅡB to Ⅳ were received adjuvant therapy according to NCCN guidelines. We also did subgroup analyses according to TNM stage.

Changes in the text: Line 157-160: After surgery, patient at stage ⅡB to Ⅳ would receive adjuvant therapy, including chemotherapy and radiotherapy. Patients with EGFR mutation would receive TKI. If enlarged lymph nodes were found during the follow-up period, patients would receive adjuvant radiotherapy.

Line 244-246: Subgroup analyses according to TNM stage indicated that patients with stage Ⅲ undergoing SV-VATS experienced higher OS and DFS than those undergoing MV-VATS. These results were not observed in patients with stage Ⅰ and Ⅱ (figure 4).

Please check Figure 4.

5. The authors need to clarify what is meant by the number of groups of N2 nodes.

Reply: Thanks for your question. The lymph nodes stage was defined as the ipsilateral mediastinal and/or subcarinal lymph node(s) according to the 7th edition of TNM classification of the International Association for the Study of Lung Cancer. N2 nodes include station 1 to 9 nodes, which are highest mediastinal nodes, upper paratracheal nodes, prevascular and retrotracheal nodes, lower paratracheal nodes, subaortic (aorto-pulmonary window), para-aortic nodes (ascending aorta or phrenic), subcarinal nodes, paraesophageal nodes (below carina), and pulmonary ligament nodes.

Changes in the text: Line 174-177: The definition of N1 and N2 was according to Mountain-Dresler modification of the American Thoracic Society (MDATS) map (24, 25).

6. As the current international guidance recommends VATS mainly for early stage cancer, it may be better to specific in their sentence in their introduction paragraph "For the past decades, the preferred surgical and anesthetic operation …..".

Reply: Thanks for your suggestion. We rewrote this sentence.

Changes in the text: Line 67-68: Since 1960, lobectomy and systematic mediastinal lymph node dissection was the gold standard for early stage lung cancer (1).

7. Interestingly, the authors have included small numbers of patients with more advanced T staging in the study who had undergone VATS resection. The authors will need to clarify if these patients received and complete any neoadjuvant or adjuvant therapy as it will affect their overall survival. It is also uncertain whether this small numbers of patients have skewed the overall results, and whether there is any merit for their inclusion especially if the numbers

were small.

Reply: Thanks for your question. All patients of stage ⅡB to Ⅳ were received adjuvant therapy according to NCCN guidelines. We also did subgroup analyses according to TNM stage.

Changes in the text: Line 157-160: After surgery, patient at stage ⅡB to Ⅳ would receive adjuvant therapy, including chemotherapy and radiotherapy. Patients with EGFR mutation would receive TKI. If enlarged lymph nodes were found during the follow-up period, patients would receive adjuvant radiotherapy.

Line 243-245: Subgroup analyses according to TNM stage indicated that patients with stage Ⅲ undergoing SV-VATS experienced higher OS and DFS than those undergoing MV-VATS. These results were not observed in patients with stage Ⅰ and Ⅱ (figure 4).

Please check Figure 4.

8. Line 149-150 seems to imply that the follow-up duration was 1 year. The authors may need to expand on their follow-up protocol after the 1st year.

Reply: Thanks for your suggestion. We're sorry for the incomplete information of follow-up protocol. We rewrote the follow-up protocol.

Changes in the text: Line 161-166: Follow-up assessment for patients occurred at a 3-months or 6-months interval during the first 2 year after the surgery, and then once a year afterwards, which included chest computed tomography (CT) scans, brain magnetic resonance imaging (MRI) scans. Telephone follow-up was conducted every year until death or July 2021. For patients who lost to follow-up, they were evaluated by the latest medical record or telephone interview.

9. It will be better to represent the x-axis of the Kaplan Meier curves in figure 2 and 3 in years after surgery rather than days.

Reply: Thanks for your advice. We represented the x-axis in figure 2 and 3 in years.

Changes in the text: Please check figure 2 and 3.

10. There were in-depth discussions about the use of anaesthetic agents, regional analgesic and reduced opioid usage with SV VATS as hypothetical reasons for the potential long-term benefits of using this technique. However, there was no details description in the methods or results section how the anaesthetic techniques differ between that of MV and SV. Certainly, there was no detail about how the techniques differed in the multi-institutional dataset. If this is the focus of discussion, there should be data within the results section to support the difference in anaesthetic agents, regional analgesic strategy and opioid usage within this cohort of patients. In modern anaesthesiology practice, it is likely that patients would have received a combination of anaesthetic and pain relief measures during and after surgery to make sure patients are comfortable. It may be difficult to attribute a specific aspect of this management as the main contributing factor.

Thanks for your question and suggestion. We didn't record the concrete consumption of anesthesia usage in this retrospective study. The specific data and information can be found in the previous RCT study in our center (Liu J, Liang H, Cui F, Liu H, Zhu C, Liang W, et al. Spontaneous versus mechanical ventilation during video-assisted thoracoscopic surgery for

spontaneous pneumothorax: A randomized trial. J Thorac Cardiovasc Surg. 2021).

Changes in the text: Line 132-133: All procedures and consumption of anesthesia were described in the previous study (18, 20, 21).

11. The authors have claimed that this was the first study looking at the long term outcomes for lobectomy after spontaneous ventilation. However, the Taiwanese group had already published their long term results using this technique around May 2021 (https://doi.org/10.1016/j.jfma.2021.04.018). The authors should include in their discussion their findings in comparison with that reported in this publication.

Reply: Thanks for your question. We included and discussed this study in discussion section.

Changes in the text: Line280-284: Chen Jin-shing et.at published the first study in terms of the long-term survival result of nonintubated thoracoscopic lobectomy earlier this year. It was demonstrated that no differences were observed in recurrence rates and overall survival between nonintubated thoracoscopic lobectomy and intubated procedure (28).

12. In a study published by the same group (doi:10.1093/ejcts/ezw160) in 2016, 9 patients from SV VATS required conversion to MV VATS. However, there were none reported in the present report. While it may be possible that those patients who had required conversion were removed because of PSM, the actual number of patients who had conversion from SV VATS to MV VATS should be included total n number, and presented in the results and figure 1. It will be interesting for the authors to share long term outcomes of these patients if possible and whether if the conversion has any adverse effects. It will be useful as well to present their reasons for their conversion, and discuss their strategies for minimise such conversions.

Reply: Thanks for your question. There were several patients from SV-VATS required conversion to MV-VATS over these years in our center. However, we didn't record these data entirely. Therefore, we didn't analyze these data.

Changes in the text: There is no change in the text.

To my knowledge this is the first study which compares long-term outcomes of non-intubated spontaneous ventilation video-assisted thoracoscopic surgery to intubated mechanical ventilation video-assisted thoracoscopic surgery. Therefore, this paper is a very important contribution in the field of non-intubated thoracic surgery.

However, there are some major corrections to do before accepting this manuscript for publication.

I would like to ask you to thoroughly review the whole manuscript again by a native or professional English speaker. Some parts are difficult to understand and there are errors in grammar and style which need corrections.

In addition, the discussion section should be reviewed for its content.

line 57: underwent = undergoing
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 57-58: Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

line 72: ..outcomes. (2), = ..outcomes (2).
Reply: Thanks for your suggestion. We have addressed that concern before.
Changes in the text: Line 67-69: Before the widely use of video-assisted thoracoscopic surgery (VATS) in 1990s, thoracotomy was the only option in thoracic surgery (2, 3).

line 73: postoperative myasthenia = ? Please explain the mechanism. Is it due to renewed postoperative metastasis?
Reply: Thanks for your advice. The postoperative myasthenia is due to the use of muscle relaxants.
Changes in the text: Line 73-78: With the growing concerns on the perioperative adverse effects caused by anesthesia, such as intubation-related airway trauma, pulmonary barotrauma, muscle relaxants related postoperative myasthenia, and postoperative nausea and vomiting, non-intubated spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS) emerged (7-9).

line 74 - 76: review English
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 73-78: With the growing concerns on the perioperative adverse effects caused by anesthesia, such as intubation-related airway trauma, pulmonary barotrauma, muscle relaxants related postoperative myasthenia, and postoperative nausea and vomiting, non-intubated spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS) emerged (7-9).

line 83: ⋯recovery. (8, 9) Our team⋯ = ⋯recovery (8, 9). Our team⋯
Reply: Thanks for your suggestion. We have addressed that concern before.
Changes in the text: Line 80-84: In 2011, the first lobectomy by the SV-VATS was reported by Chen et al. (11), demonstrating its feasibility and safety. At present, there are many studies on the perioperative outcomes of the SV-VATS compared to the MV-VATS, revealing that the SV-VATS exhibits a shorter postoperative hospital stay and a faster postoperative recovery (12, 13).

line 85: ⋯reconstruction. (10-13) = ⋯reconstruction (10-13).
Reply: Thanks for your suggestion. We have addressed that concern before.
Changes in the text: Our team also demonstrated the application of the SV-VATS for lobectomy and even carinal reconstruction in our previous studies (14-17).

line 86: ..moving mediastinal..= ..moving of mediastinal..
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 89-92: Because of the relatively unstable operation field and moving of mediastinal structures, some researchers may question whether the systematic lymph node dissection under the SV-VATS is eligible and long-term outcomes compared to MV-VATS (11).

line 88: ⋯eligible. (7) = ⋯eligible (7).
Reply: Thanks for your suggestion. We have addressed that concern before.
Changes in the text: Line 89-92: Because of the relatively unstable operation field and moving of mediastinal structures, some researchers may question whether the systematic lymph node dissection under the SV-VATS is eligible and long-term outcomes compared to MV-VATS (11).

line 90: ⋯attempt to ..= ⋯attempted to ..
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 96-97: Therefore, we attempted to explore the superiority of the SV-VATS over the MV-VATS in the long-term survival among patients with NSCLC.

line 97: ⋯involved..   = ⋯included ⋯.
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 103-107: All patients with NSCLC who went through pulmonary surgery between 2011 and 2018 in the First Affiliated Hospital of Guangzhou Medical University were consecutively recruited in the retrospective database (database 1), which included 6821 patients (6133 MV-VATS and 688 SV-VATS).

line 100: ⋯gained⋯= ⋯obtained⋯
Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 107-109: The study protocol and methods were reviewed by the institutional ethics committee of the First Affiliated Hospital of Guangzhou Medical University (2020-69). Informed consent was obtained from each patient before inclusion.

line 102 to 124: please review English for errors in grammar and style with a native or professional English speaker

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 110-111: Patients were included for recruitment into the database, if they met the following criteria:

line 124: Anesthesia and Surgery Management = Anesthesia and Surgical Management

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 131: Anesthesia and Surgical Management

line 125: All anesthesia process was described···= ? What do you mean by "process"? Do you mean anesthesia protocol?

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 132-133: All procedures and consumption of anesthesia were described in the previous study (18, 20, 21).

line 127: double-laryngeal disposable mask airway = ? Do you rather mean Double Lumen Laryngeal Mask Airway?

Reply: Thanks for your suggestion. We're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 134-135: The double-lumen tracheal intubation was substituted as a double lumen laryngeal disposable mask airway.

line 129: LMA, please explain abbreviation (LMA = laryngeal mask airway)

Reply: Thanks for your advice. We're sorry that we didn't write the abbreviation and added it in the text.

Changes in the text: Line 135-140 Also, a nasal cannula or facial mask could sometimes be a substitute for LMA (laryngeal mask airway), depending on different situations of patients. Muscle relaxant was not administered, while intravenous sedative (propofol) was sufficiently administered. Intravenous analgesics, which was mostly opioid, including remifentanil and sufentanil, was significantly reduced.

line 130: "···was entirely administered". What do you mean by "entirely"? Entirely = elusively?, only propofol was administered?

Reply: Thanks for your suggestion. We're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 135-140 Also, a nasal cannula or facial mask could sometimes be a substitute for LMA (laryngeal mask airway), depending on different situations of patients.

Muscle relaxant was not administered, while intravenous sedative (propofol) was sufficiently administered. Intravenous analgesics, which was mostly opioid, including remifentanil and sufentanil, was significantly reduced.

line 129 -130: please review English for errors in grammar and style with a native or professional English speaker

line 132: "sharply" =? Do mean "significantly" and in relation to what? In relation to which other type of anesthesia?

Reply: Thanks for your advice. We're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 135-140 Also, a nasal cannula or facial mask could sometimes be a substitute for LMA (laryngeal mask airway), depending on different situations of patients. Muscle relaxant was not administered, while intravenous sedative (propofol) was sufficiently administered. Intravenous analgesics, which was mostly opioid, including remifentanil and sufentanil, was significantly reduced.

line 136: During operation = perioperatively

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 144-147: Perioperatively, end-tidal carbon dioxide partial pressure, pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG), and noninvasive blood pressure were routinely measured and continuously monitored both in the SV-VATS group and the MV-VATS.

line 138: ···continually··· = continuously

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 144-147: Perioperatively, end-tidal carbon dioxide partial pressure, pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG), and noninvasive blood pressure were routinely measured and continuously monitored both in the SV-VATS group and the MV-VATS.

line 140: ···and avoid··· = ···and to avoid···

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 147-149: To ensure that patients were at a sufficient depth of anesthesia and to avoid intraoperative awareness and excessive sedation, the Bispectral Index (BIS) was monitored and maintained at 40-60 under the SV-VATS.

line 142 - 143: ..progress= ?···please review English for errors in grammar and style with a

native or professional English speaker

Reply: Thanks for your advice. We 're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 150-151: The standard NSCLC radical surgery procedure, including lobectomy and lymph node dissection, was the same in both anesthesia methods.

line 145- 146: ⋯were the same as the previous study.. = ⋯were the same as in the previous study⋯ What do you mean by the same? Could you go into more details so that someone who does not know the study can understand what you want to explain?

Reply: Thanks for your suggestion. The surgical procedure and methods of lobectomy were detailed described in the previous study in our center and others.

Changes in the text: Line 153-155: The surgical procedure and methods of lobectomy and dissection of N1 as well as N2 were the same as in the previous study in our center (22), and studies reported by Scott J Swanson et al. (4) and Shigemura et al. (23).

line 149 - 151: please review English for errors in grammar and style with a native or professional English speaker

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 161-164: Follow-up assessment for patients occurred at a 3-months or 6-months interval during the first 2 year after the surgery, and then once a year afterwards, which included chest computed tomography (CT) scans, brain magnetic resonance imaging (MRI) scans.

lines 155 - 181: This part needs to be reviewed for errors in English grammar and style with more fluency by a native or professional English speaker

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 168-170: The baseline information of these patients was recorded. The perioperative and survival data were collected using a combination of electronic data record system and telephone interview.

line 184: ..understood the SV-VATS.. = ..understood SV-VATS..

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 201-202: In order to further explore the long-term benefit of the SV-VATS, we compared the OS of patients with NSCLC who underwent SV-VATS, MV-VATS and thoracotomy.

line 184: ..understood the MV-VATS.. = ..understood MV-VATS..

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We

corrected the sentence.

Changes in the text: Line 201-202: In order to further explore the long-term benefit of the SV-VATS, we compared the OS of patients with NSCLC who underwent SV-VATS, MV-VATS and thoracotomy.

line 188: ..were recruited.. = ···were also recruited..

Reply: Thanks for your suggestion. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 205-206: Patients with invasive lung adenocarcinoma confirmed by postoperative pathology were also recruited.

line 189: the SV-VATS and the MV-VATS.. = ..experienced SV-VATS and MV-VATS

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 206-209: PSM was used to match patients who experienced thoracotomy with those who experienced SV-VATS and MV-VATS, and the survival information was compared by Kaplan-Meier and log-rank test.

line 189: ..compared the ···   = ..compared to the survival ···

Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.

Changes in the text: Line 206-209: PSM was used to match patients who experienced thoracotomy with those who experienced SV-VATS and MV-VATS, and the survival information was compared by Kaplan-Meier and log-rank test.

line 215-216: "The median survival time of the SV-VATS or the MV-VATS group was not reached." = ? What do you mean by "reached"? What is the "target" which should be reached?

Reply: Thanks for your advice. We're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 234-245: The median survival time of the SV-VATS or the MV-VATS group cannot be calculated.

line 225: ..status of anesthesia methods..= What do you mean by "status"?

line 227: ..status of gender..= What do you mean by status of gender? Please review wording by a native English speaker

line 229 and 231: status of anesthesia = ? see same as above line 225

Reply: Thanks for your advice. We're sorry that you can't understand what we tried to expressed. We changed the expression.

Changes in the text: Line 247-253: Variables, including the mode of anesthesia methods (p=0.015), T stage (p<0.001), N stage (p<0.001), and TNM stage (p<0.001) were significant prognostic factors for DFS by univariate Cox analysis, and T stage (p<0.001), and N stage (p<0.001) were significant prognostic factors for OS. Additional multivariate analysis indicated that mode of anesthesia methods (p=0.001), and T stage (p=0.015) were independent factors for DFS, and mode of anesthesia methods (p=0.004), and T stage (p=0.037), were independent factors for OS (Table3).

line 235 - 240 This part needs to be reviewed for errors in English grammar and style with more fluency by a native or professional English speaker
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 255-261: For three-group comparison, according to the inclusion and exclusion criteria, there were 6451 patients enrolled in our study, including 2533 patients undergoing thoracotomy in database 2, 3711 patients undergoing the MV-VATS in both databases, and 210 patients who underwent the SV-VATS in database 1 (Figure 1). After a 1:1:1 PSM, 582 (194:194:194) patients remained. Features and baseline information of all patients before and after 1:1:1 PSM were displayed in Table 4. The median survival of the SV-VATS and the MV-VATS was not reached.

Comment on the discussion section:
lines 249 - 314: The whole part needs to be reviewed and rewritten for errors in English grammar and style with more fluency by a native or professional English speaker. It should also be discussed with the linguistic expert whether some sentences should be written in the present tense rather than in the past tense.
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Please check in the text.

Concerning lines 287 - 302, this part could be shortened and written in a more compact way.
Reply: Thanks for your advice. We changed some of the expression in this paragraph.
Changes in the text: Line 312-327: Propofol-TIVA (total intravenous anesthesia) was suggested to a higher OS in patients having cancer removal surgery (41). There were several in-vitro studies showed a pro-metastatic impact of volatile anesthesia and an antimetastatic impact of intravenous anesthesia (42, 43). Iwasaki M et al. (44) pointed that volatile anesthesia changed tumors environments and influenced the apoptosis of tumor cells. Zhang D et al. (45) found that apoptosis of tumor cells existed, and cell proliferation was reduced when tumor cells were exposed to propofol. A meta-analysis assumed that the usage of TIVA in operation is related to improved RFS and OS in NSCLC and breast cancer compared with volatile anesthesia (41). In patients with digestive tract surgery, an observational study demonstrated a contrary result that there was no difference in OS and RFS between volatile

and intravenous anesthesia (46). A retrospective cohort study showed that the relationship between different anesthesia use and long-term survival outcome of breast cancer was weak (47). In our study, TIVA was administered in the SV-VATS group. We hypothesized TIVA may contribute to the positive long-term outcome in the SV-VATS compared to the MV-VATS, which warrants future studies to add clarity in contradictory findings from the current studies.

lines 305 - 312: as above, English should be reviewed.
Reply: Thanks for your advice. We're sorry for the mistake of grammar and language. We corrected the sentence.
Changes in the text: Line 328-338: There are some limitations in our study. First, there may have been selection bias despite the use of 1:1 or 1:1:1 PSM, as patients were not randomized before the surgery and the majority of patients undergoing MV-VATS or thoracotomy were excluded after PSM in our analysis. Second, as the technique of the SV-VATS was not mature at the beginning of application, the difference in experience of surgeons may bring potential bias. Third, the sample size was not large enough. There were 400 patients included after PSM in this retrospective analysis. Besides, the follow-up time was not long enough. Though we followed up two groups of patients for more than 4 years on average, the follow-up time was not long enough to calculate the median survival time of SV-VATS. Further RCT studies and multicenter prospective observational studies need to be developed to confirm the survival advantages in the SV-VATS.

line 311: "Though we followed up two groups of patients more than 4 years on average, the follow-up time was still not long enough for the median survival time of SV-VATS." NB.: please correct "….patients more than 4 years …" = patients for more than 4 years
Do you mean the follow-up time was still not long enough to calculate the median survival of SV-VATS? What do you want to say in this phrase?
Reply: Thanks for your questions and advice. Postoperative myasthenia is one of the common postoperative complications for the use of muscle relaxant during anesthesia and operation. We rewrite the grammars and places that you don't understand. We hope the rewriting would make it easier to understand. Please check in the text.
Changes in the text: Please check in the text.

In your retrospective study, you conclude that there is a superiority in survival in patients undergoing SV-VATS compared to MV-VATS.
Factors which could explained for better survival in the SV-VATS group are listed up in the discussion section and include use of opioids in the two anesthetic techniques (SV-VATS and MV-VATS), the use of regional anesthesia in the SV-VATS group, propofol- TIVA anesthesia increasing overall survival (OS) compared to volatile agents.
You mentioned well "Anesthesia methods" in table 3, but one cannot see whether the different anesthetic techniques have been compared in detail between groups (SV-VATS and MV-VATS) and whether they could contribute to better OS. However, for non-intubated lung

surgery, in many papers, TIVA has also been used in MV-VATS and vice versa volatiles have also been used in SV-VATS (see pubmed). Therefore, it is not clear if anesthetic technique contributed to a better OS as you did not compare TIVA and volatile anesthetics in SV-VATS and MV-VATS.

Reply: Thanks for your question and suggestion. We didn't record the concrete consumption of volatile and TIVA in this retrospective study. The specific data and information can be found in the previous RCT study in our center (Cui F, Xu K, Liang H, Liang W, Li J, Wang W, et al. Spontaneous ventilation versus mechanical ventilation during video-assisted thoracoscopic surgery for spontaneous pneumothorax: a study protocol for multicenter randomized controlled trial. J Thorac Dis. 2020;12(4):1570-81).

Changes in the text: Line 132-133: All procedures and consumption of anesthesia were described in the previous study (18, 20, 21).

Other points should also be mentioned in the discussion section in order to help explaining the better OS in SV-VATS patients such as the use of positive inspiratory pressure ventilation in MV-VATS compared to negative inspiratory pressure during spontaneous ventilation in SV-VATS, also postoperative complications following SV-VATS and MV-VATS which could probably explain a better OS for SV-VATS.

In addition, could microbarotrauma in MV-VATS be a reason for less OS? Could MV-VATS depress more immunity than SV-VATS?

Are SV-VATS patient earlier ambulated, quicker mobilised and on their feet and eating earlier than MV-VATS patients which could help to improve immune response and decrease cancer recurrence?

Reply: Thanks for your question. We agreed that the hypothesis you pointed out may own to better OS for SV-VATS. However, the scientific evidence may not be insufficient. Therefore, we didn't include them in this study.

Changes in the text: There is no change in the text.

Is the comparison between groups as shown in table 1 biased as patients in the SV-VATS group are younger and have less weight (less obesity)?

Reply: Thanks for your question. The age and BMI of the group SV-VATS and MV-VATS were significantly different before PSM. However, after PSM, the age and BMI were the same between two groups.

Changes in the text: There is no change in the text.

Are patients surgically more complicated in the MV-VATS group as the mean lymph node resection is 12.04 compared to 10.91 in the SV-VATS group?

Reply: Thanks for your question. It is more complicated surgically in SV-VATS, so it made sense that the group number of N2 station lymph nodes in the SV-VATS group are less than the MV-VATS group (2.63 ± 1.11 vs. 3.03 ± 1.18, p=0.001). Besides, the number of N2 station were the same between the SV-VATS and the MV-VATS group (10.91 ± 8.35 vs. 12.04 ± 7.83, p=0.162).

Changes in the text: There is no change in the text.

Lines 317 - 318: Conclusion section:

Invasive NSCLC patients underwent SV-VATS lobectomy were associated with 318 better long-term outcomes compared with MV-VATS and thoracotomy. = Invasive NSCLC patients undergoing SV-VATS lobectomy were associated with better long-term outcomes compared to MV-VATS and patients undergoing thoracotomy.

Reply: Thanks for your advice. We rewrite the conclusion part.

Changes in the text: Line 57-58: Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.