Peer Review File

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We would like to thank all the reviewers for the constructive feedback. We have addressed all the reviewers' comments and made necessary modifications accordingly. Detailed revisions and responses to each comment are provided below. In this study, we attempted to verify the consistency between expected and postoperative function loss actually observed after VATS pulmonary resection in good-risk patients, and explored which segmental resections would be superior to its corresponding lobectomy in pulmonary function preservation for good-risk patients.

Then we innovatively used the resection extent index to evaluate the pulmonary function changes after thoracoscopic lobectomy and thoracoscopic segmentectomy. Propensity-score matching was used for the first time to compare functional changes after segmentectomies to their corresponding lobectomies. We believe the results of the study are helpful for better selection of appropriate resection extent to benefit more patients with early stage lung cancers. We hope that with the help from all the reviewers, our revised manuscript could be considered for publication in TLCR.

Reviewer A

The paper was well written and easy to follow, and I read it with great interest. The

data in the results and drawing conclusion were reasonable and self-explanatory. Only a few concerns should be addressed as follow:

Comment 1: Postoperative pulmonary function is affected by postoperative complication such as prolonged air leakage requiring pleurodesis and pneumonia/ pneumonitis. The incidence rate related to segmentectomy like prolonged air leakage should be clarified in the manuscript.

Reply 1: Thank you for this comment. In this study, patients who underwent severe postoperative complications have also been excluded, such as bronchopleural fistula, respiratory failure, pulmonary embolism, et al. To the best our knowledge, few studies have ever discussed the influences on postoperative pulmonary function from postoperative complications, such as prolonged air leakage or pneumonia/pneumonitis (1,2). In the JCOG0802/WJOG4607L trial, postoperative complications were not taken into account when reporting the pulmonary function changes (3).

Recently, Maeyashiki et al found that the benefit of segmentectomy compared to lobectomy for pulmonary function preservation was impaired by chemical pleurodesis for prolonged air leakage (1). However, in this study, patients suffering prolonged air leakage (an air leak lasting for more than 5 days) were treated with autologous blood pleurodesis (n=8, 1.2%, 7 cases of lobectomy and one case of segmentectomy) (4). Previous study has pointed out that autologous blood pleurodesis has less influences on pulmonary function changes compared with talc powder and tetracycline (2). Therefore, whether pulmonary function is affected by prolonged air leakage treated

with autologous blood pleurodesis remains unclear. No significant difference in postoperative pulmonary function changes could be detected between patients with autologous blood pleurodesis and those without autologous blood pleurodesis (FVC: P=0.160; FEV1: P=0.563; DLCO: P=0.074) in the current study. Thus, we consider it better to mention the influences on pulmonary function changes from postoperative complications in the Limitation in the Discussion.

Changes in the text: We have added a flow chart of enrollment and exclusion (see Figure 1 in the revised manuscript). We have revised the sentences as "Patients who suffered severe postoperative complications were not included, such as bronchopleural fistula, respiratory failure, pulmonary embolism, et al. And those who had inadvertent phrenic nerve injury during surgery were also not included" (see Page 7, Line 102-104 in the Methods). We also added the incidence of pleurodesis in this study (see Page 27, Table 1). And we have added the sentence "Meanwhile, whether the pulmonary function changes are affected by the postoperative complications such as prolonged air leakage, which is treated with autologous blood pleurodesis in the current study remains unclear." (see Page 17, Line 281-283 in the Limitation in the Discussion).

Comment 2: The more detailed indications for segmentectomy should be described, as to minimize locoregional recurrence as well as to preserve lung functions. The appropriateness for the indication of segmentectomy should be clarified with the incident data of locoregional recurrence.

Reply 2: Thank you for the comment. In this study, the indications for intentional segmentectomy follow the National Comprehensive Cancer Network (NCCN) guideline, which are peripherally located nodules less than 2 cm with at least one of the following factors: pure AIS histology, nodule has ≥50% ground-glass appearance on CT, radiologic surveillance confirms a long doubling time (≥400 days) (5). Meanwhile, the current study put more emphasis on the postoperative pulmonary function changes after lobectomy and intentional segmentectomy, instead of on the long-term oncological outcomes such as locoregional recurrence.

Changes in the text: We have described the detailed indications for segmentectomy in the revised manuscript, "The indications for intentional segmentectomy in the current study followed the National Comprehensive Cancer Network guideline, which were peripherally located nodules ≤2 cm whereby a safe resection margin could be achieved by sublobar resection, together with at least one of the following factors: pure adenocarcinoma in situ, nodules with ≥50% ground-glass appearance on computed tomography, radiologic surveillance confirmed a long doubling time (≥400 days)." (see Page 7-8, Line 106-111 in the Methods).

Comment 3: Does this study exclude cases with subsegmentectomy?

Reply 3: Yes, this study excluded subsegmentectomy. In this study, we compared only the pulmonary function changes after lobectomy and after segmentectomy.

Changes in the text: No change made.

Reviewer B

This study is a prospective study aimed to evaluate postoperative respiratory function preservation using spirometry for stage IA lung cancer.

This study is very well planned and organized. However, there are some problems, and I would like to point out these problems in order to improve the quality of the paper.

Major problems

Comment 1: Please explain the indication of segmental resection in more detail. In JCOG0802/WJOG4607L trial, they include maximum tumor diameter of ≤2 cm and the proportion of the maximum diameter of the tumor itself to consolidation is >25%.

Reply 1: Thank you for the comment. In this study, the indications for intentional segmentectomy follow the National Comprehensive Cancer Network (NCCN) guideline, which are peripherally located nodules less than 2 cm with at least one of the following factors: pure AIS histology, nodule has ≥50% ground-glass appearance on CT, radiologic surveillance confirms a long doubling time (≥400 days) (5).

Changes in the text: We have explained the detailed indications for segmentectomy in the revised manuscript, “The indications for intentional segmentectomy in the current study followed the National Comprehensive Cancer Network guideline, which were peripherally located nodules ≤2 cm whereby a safe resection margin could be achieved by sublobar resection, together with at least one of the following factors: pure adenocarcinoma in situ, nodules with ≥50% ground-glass appearance on computed tomography, radiologic surveillance confirmed a long doubling time (≥400

days).” (see Page 7-8, Line 106-111 in the Methods).

Comment 2: Postoperative follow-up should be mentioned in Method. Is there any postoperative rehabilitation intervention? Postoperative activity might make a difference in postoperative pulmonary function.

Reply 2: Thank you for your comment and suggestion. We have mentioned the postoperative course and follow-up in the revised manuscript.

Changes in the text: We have added the sentences “After the surgery, all the patients were encouraged to become ambulatory and do the respiratory function training, and they were discharged with good lung expansion. No reoperation or readmission occurred in patients included in this study. And the postoperative surveillance included check up of recovery and evaluation of potential adjuvant therapies one month after surgery, chest CT scan, serum tumor markers, neck and abdominal ultrasonography performed every 6 months during the first two year and then annually.” (see Page 8, Line 117-123 in the “Postoperative course and follow-up” section in the Methods).

Comment 3: Please present preoperative pulmonary function data.

Reply 3: Thank you for the suggestion. We have added the preoperative pulmonary function values in the revised manuscript.

Changes in the text: We have added the preoperative pulmonary function values (see Page 26, Table 1). And we have added the sentence “No significant difference was

detected in the baseline pulmonary function between the two groups (FVC: P=0.079; FEV1: P=0.128; DLCO: P=0.533)" (see Page 12, Line 179-180 in the Results).

Comment 4: What does the P-value represent in Supplementary Table 1.

Reply 4: The P-value in Supplementary Table 1 represent the difference of tumor location between lobectomy and segmentectomy.

Changes in the text: We have explained the P-value by adding the sentence "*P-value for the difference in tumor location between lobectomy and segmentectomy." in the footnote of Supplementary Table 1 (see Page 35, Line 465).

Comment 5: You need more discussion about Resection extent index. What do you think about the difference in Resection extent index between left and right S9 + 10?

Reply 5: Thank you for this comment. Different from the previous studies, ours compared the pulmonary function changes after VATS segmentectomy with those after the corresponding VATS lobectomy, and then the resection extent index was introduced. Therefore, it makes no sense to evaluate the difference in pulmonary function changes after left and right S_{9+10} resection using the resection extent index, which should be used to evaluate the difference between left S_{9+10} resection and left lower lobectomy, or the difference between right S_{9+10} resection and right lower lobectomy.

Changes in the text: We have revised the sentences as "In addition, we further investigated which VATS segmental resections would be truly superior to its

corresponding VATS lobectomy in pulmonary function preservation" (see Page 6, Line 80-82 in the Introduction), "To explore which VATS segmentectomies might be functionally beneficial than its corresponding VATS lobectomies, resection extent index was introduced to evaluate the loss of parenchyma and pulmonary function after surgery." (see Page 16, Line 258-260 in the Discussion), "To our knowledge, this is the first prospective observational study comparing pulmonary function changes according to different resection extent indexes after VATS lobectomy and its corresponding VATS segmentectomy solely in good-risk patients." (see Page 16, Line 268-270 in the Discussion).

Comment 6: RUL S1 + S2 resection is 0.67 of Resection extent index, which is not recommended for segmental resection, but LUL S1 + 2 is 0.25, which is within the recommended range.

The extent of the resected area is similar but Resection extent index is different, because the size of the excised lung lobe is different. It is not enough to consider only the resected lobe, and it is necessary to consider the remaining lobe other than the resected lobe.

Reply 6: Thank you for the comment. And this is exactly our consideration on potential functional benefit of segmentectomy. In this study, we introduced the resection extent index, which took into account the influence from the size of the excised lobe when evaluating the pulmonary function preservation after segmentectomy.

Changes in the text: No change made.

Comment 7: Supplementary table 3 is poor table. It is not acceptable.

Reply 7: Thank you for the comment. Supplementary Table 3 were used to demonstrate the differences between our study and previous studies on pulmonary function in the VATS setting. Now we have deleted this table, and referenced all the previous studies in the Discussion.

Changes in the text: We have deleted Supplementary Table 3, and referenced all the studies which were mentioned in Supplementary Table 3 (see Page 15, Line 237-240).

Comment 8: The evaluation of blood flow is clinically essential. Because the preserved lung function should be considered to be made up of not only pulmonary function but also blood flow. The authors should provide the data of distribution of blood flow.

Reply 8: Thank you for the comment. The evaluation of blood flow was not conducted in the current study, as it was not included in the study design. All the patients included in this study were all good-risk patients, for whom the evaluation of blood flow might be not necessary (6-8). Therefore, we added this to the Limitations in the Discussion.

Changes in the text: We have revised the sentences as “The purpose for this study was to evaluate the functional benefits of segmentectomy as an intentional procedure for good-risk patients. Patients who had poor lung function were excluded during the

study design. Therefore, quantitative ventilation-perfusion scans would be not essential in this study, and the results could not be extrapolated to patients with poor lung function." (see Page 17, Line 275-279 in the Discussion).

Reviewer C

This a non randomized prospective study comparing the post-operative pulmonary functions between VATS lobectomy and segmentectomy. This study is well-written and well-conducted. The conclusion is correct based on your results.

Some minor comment:

Comment 1: Did you analyse the difference between upper and lower lobe? we know that the perfusion is generally more important in the lower part.

Reply 1: Thank you for the comment. We have compared the pulmonary function changes between the resections in upper lobe and lower lobe (see the table below). Significant differences were detected in FVC and DLCO loss after lobectomy on the right side, and DLCO loss after segmentectomy on the right side. No difference was detected in the pulmonary function changes after lobectomy or segmentectomy on the left side. But numbers of segmentectomy and lobectomy were not equally distributed on the left or the right sides, nor in the upper or lower lobes. It is for this reason that we did a propensity score matching by comparing segmentectomies and their corresponding lobectomies in this study.

Pulmonary function changes	Upper lobe	Lower lobe	P-value

Right side			
Lobectomy	N=166	N=75	
FVC loss (%)	-16.5±10.7	-19.8±10.4	0.025
FEV1 loss (%)	-18.8±10.7	-18.4±9.8	0.759
DLCO loss (%)	-11.3±12.9	-16.9±12.2	0.002
Segmentectomy	N=78	N=50	
FVC loss (%)	-10.5±9.3	-11.0±8.0	0.781
FEV1 loss (%)	-12.8±8.5	-13.0±7.3	0.907
DLCO loss (%)	-8.0±11.1	-13.3±15.9	0.031
Left side			
Lobectomy	N=48	N=49	
FVC loss (%)	-16.6±12.3	-20.4±8.1	0.073
FEV1 loss (%)	-18.7±12.4	-20.1±8.6	0.538
DLCO loss (%)	-13.3±12.4	-16.3±13.9	0.282
Segmentectomy	N=157	N=36	
FVC loss (%)	-13.2±8.5	-11.7±7.5	0.325
FEV1 loss (%)	-16.2±7.5	-13.4±11.1	0.065
DLCO loss (%)	-9.9±11.7	-9.6±10.4	0.873

Changes in the text: No change made.

Reviewer D

Pulmonary function change after thoracoscopic lobectomy versus segmentectomy is

an important research topic among thoracic surgeons. This manuscript describes a well-designed prospective study of the relatively large cohort of lung cancer patients operated by the single team at the single institution. Propensity score matching is appropriately used as randomization is difficult.

Although novel evaluation methods (3D-CT volumetry or Single Photon Emission CT) are not used, your results are clear and will be of interest to readers. I agree with you that pulmonary function loss after VATS lung resection is not in direct proportion with the extent of resection (the number of resected segments).

I need to indicate several issues like below, but I hope these will help you in improving your article.

Comment 1: Patient selection

The number of the patients who received lung cancer surgery during the same period, and of the patients excluded with their respective reasons should be made clear. I think a "flow chart of patients enrollment and exclusion" is suitable for this purpose.

Reply 1: Thank you for the comment. We have added a flow chart of patients enrollment and exclusion as suggested.

Changes in the text: We have added a new figure (see Figure 1 in the revised manuscript) with its legend.

Comment 2: Operative technique

Pleural coverage with the absorbable mesh and/or fibrin glue are widely used

especially in segmentectomy. Routine use of these techniques, or the frequency of the application of these technique may potentially affect lung expansion and pulmonary function afterwards.

Reply 2: Thank you for the comment. Pleural coverage with the absorbable mesh or fibrin glue was not commonly used in this study. To prevent postoperative prolonged air leak, we would suture the pleural edge (pleural suture) if severe air leak was detected intraoperatively during the air-tightness test, which did not impair the pulmonary function preservation comparing to pleural coverage with the absorbable mesh or fibrin glue (9,10). Few studies have ever discussed the influence on pulmonary function recovery from the pleural suture. In this study, pleural suture for airleak was used similarly after segmentectomy and lobectomy. Therefore, we consider that the results would not be affected.

Changes in the text: No change made.

Comment 3: Post-operative course of the patients

The average length of drainage period and the frequency of pleurodesis or re-operation should be provided as a part of patient characteristics (Table 1).

Reply 3: Thank you for the comment. No reoperation or readmission occurred in patients included in the current study. We have also added the average length of drainage period and the incidence of pleurodesis in Table 1.

Changes in the text: We have added the sentences “After the surgery, all the patients were encouraged to become ambulatory and do the respiratory function training, and

they were discharged with good lung expansion. No reoperation or readmission occurred in patients included in this study. And the postoperative surveillance included check up of recovery and evaluation of potential adjuvant therapies one month after surgery, chest CT scan, serum tumor markers, neck and abdominal ultrasonography performed every 6 months during the first two year and then annually." (see Page 8, Line 117-123 in the "Postoperative course and follow-up" section in the Methods). And we have added the duration of chest tube drainage and the incidence of pleurodesis (see Page 26, Table 1).

Reference:

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