

## Peer review file

Article information: <http://dx.doi.org/10.21037/jtd-20-3325>

### Reviewer A

Comment 1. The authors should show how long were intervals between first and second surgery and how many people had the contralateral tumors progressing after the first surgery in the staged resection group.

Reply 1: Thank you for your question. The time of the second operation was based on each patient's recovery condition and high-resolution CT after surgery. In our study, the median interval between the first and second lobectomies was 7 months, with a range of 2 to 22 months.

During follow-up, 7 patients had the contralateral tumors progressing after the first surgery in the staged resection group, of which 2 patients had distant metastasis detected at 8 months and 11 months by PET-CT postoperatively.

Changes in the text: We have changed the results and the discussion of the track changes version.

Comment 2. Postoperative chest pain disturbing the cough causes atelectasis after lung resections. How did the authors manage postoperative pain?

Reply 2: Thank you for your question. An intravenous analgesia pump and postoperative ward analgesia program, and preventive antiemetic were routinely applied in the post anesthesia recovery room.

Changes in the text: We have changed the line 130 to 132 of the track changes version.

Comment 3. The percentages of patients with p-IA PLC are 56% for the simultaneous group and 29% for the staged group. In this study, the rates are not significantly different. I think that it is a type II error because of the small case number. Did the tumorous condition impacted on the DFS.

Reply 3: Thank you for the helpful comment. The main reason that the stage IA patients

in the staging operation group is less than the patients with the simultaneous group is that some patients in the stage operation have tumor progression in the interval between operations, which makes the number of stage IA patients in the stage operation group less than the simultaneous group. At the same time, whether the condition of the tumor affects DFS needs further investigation in the future.

Comment 4. What was the node positive on PET-CT? This issue should be described in detail.

Reply 4: Thank you for pointing out our mistake. We just want to exclude mediastinal lymphatic metastases by CT. We have deleted it because of our pen error.

Comment 5. Why was the left lower lobe divided into 4 segments as same as the left upper lobe? Usually, LLL has not median basilar segment (seg. 7).

Reply 5: Thank you for your comment. The number of segment resections were calculated as described by Zeiher and colleagues. (Zeiher BG, Gross TJ, Kern JA, et al. Predicting postoperative pulmonary function in patients undergoing lung resection. Chest 1995;108:68-72).

Comment 6. In Surgical technique, what was the total cost? Did it include the fee of anesthesia, room and drugs?

Reply 6: Thank you for the helpful comment. The total cost including the fee of surgical, anesthesia, room and drugs.

Comment 7. OS and DFS were defined as the time from the operation to the last follow-up. In the staged group, which does the operation mean the first operation or the second operation?

Reply 7: Thank you for the helpful comment. In the staged group, OS and DFS were defined as the time from the first operation.

Change in the text: The revised part can be found in line 139 to 142 of the track changes version.

Comment 8. How frequently did the patients receive CT after surgery? What was the routine follow-up?

Reply 8: Thank you for the helpful comment. In our study, patients were recommended to repeat CT and pulmonary function test at the 1, 3, 6 and 12 months during the first 2 years after operations. Follow-up data were obtained from telephone calls, or direct outpatient examinations.

Change in the text: The revised part can be found in line 134 to 139 of the track changes version.

Comment 9. Is the time required for repositioning and disinfection excluded from the total operating time in the simultaneous group? I think that total operative time is usually longer in the simultaneous group than the staged group even if it did not include the time required for repositioning and disinfection. Why did the result occur? The reasons should be shown in Discussion.

Reply 9: The time of reposition and disinfection were not included in the total operating time in the simultaneous group. The reason for the increased time is that the second operation is technically demanding to safely handle the changed hilum structure caused by the last operation.

Comment 10. In conclusion, the authors described that Simultaneous resection has significant advantages compared to staged resection, including better DFS and OS and reductions in cost, total operative time and hospital stays. However, there were no differences between the two groups in all patients. So, the OS should be removed.

Reply 10: Thank you for your suggestion. We have changed our conclusion about OS in all patients. In the study, simultaneous resection had a significantly better OS than staged resection for those patients with bilateral pure solid nodules or tumor size > 3 cm.

Change in the text: The revised part can be found in line 324 to 326 of the track changes version.

Comment 11. Since simultaneous bilateral lobectomy resection with RLL+LUL and RLL+LLL were high risk for respiratory failure, these resections should be avoided. The authors should show the indications of these resections in your institution.

Reply 11: In our institution, based on the respiratory examination, those patients with vital capacity (VC) > 4.0L, a forced expiratory volume in 1 s (FEV1) > 2.5 L, and the predicted FEV1 >1.8 L, was thought to have good tolerance to undergo RLL+LUL or RLL+LLL simultaneously. Then, a bilateral thoracoscopic approach was planned to minimize the invasiveness as much as possible. Some previous studies also reported that the recommended value of FEV1 for safe resection was more than 2 L for pneumonectomy and more than 1.5 L for lobectomy. Later guidelines added that for lobectomy and pneumonectomy, FEV1 and DLCO should be more than 80% of the predicted value. Therefore, for those patients with FEV1 less than 80% or FEV1 less than 2L, simultaneous bilateral lobectomy resection was not recommended.

Reference:

1. BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. Thorax 2001;56:89-108.
2. Colice GL, Shafazand S, Griffin JP, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 2007;132:161s-77s.
3. Zeiher BG, Gross TJ, Kern JA, et al. Predicting postoperative pulmonary function in patients undergoing lung resection. Chest 1995;108:68-72.

Change in the text: The revised part can be found in line of the track changes version.

Comment 12. By what were the OS and DFS curves analyzed? Log-rank test or Wilcoxon test others? The method should be described in Statistical analysis.

Reply 12: Thank you for your suggestion. OS and DFS were estimated by the Kaplan-Meier estimation using the log-rank test.

Change in the text: The revised part can be found in line 150 to 152 of the track changes version.

Comment 13. In Patient characteristics, the values regarding age should be described with a one decimal place.

Reply 13: Thank you for the useful suggestion, a one decimal place of the age was added in the table1.

Change in the text: The revised part can be found in table 1 of the track changes version.

Comment 14. In discussion, the second operation was usually performed about 2 to 4 months after the first one, even if postoperative recovery went smoothly. These data should be described in Results.

Reply 14: Thank you useful suggestion. These data had been described in results.

Change in the text: The revised part can be found in 201 to 241 line of the track changes version.

Comment 15. On page 12, line 230, Takahiro is the first name, and it should be changed to Iida.

Reply 15: Thank you for pointing out our mistake. We have corrected the sentence.

Change in the text: The revised part can be found in line 261 of the track changes version.

Comment 16. Many mistakes of % values are in Table 1. They should be revised: Line "Preoperative comorbidities", the data of Cardiopathy 4 (5%) to 4 (6%), Line "Preoperative comorbidities", the data of Hypertension 4 (19%) to 4 (10%), Line "Size of the largest tumor, mm", the data of >3 16 (49%) to 16 (39%).

Reply 16: Thank you for pointing out these mistakes. We have corrected those date in Table 1 and checked the whole manuscript carefully.

Change in the text: The revised part can be found in Table 1 of the track changes version.

Comment 17. In Table 2, Line "Pathologic stage", the data of Staged bilateral lobectomy resection are incorrect.

Reply 17: Thank you for the useful comment. In the study, pathological staging was based on the most advanced stage of all lesions according to the 8th edition of the TNM staging system for lung cancer.

Comment 18. In Table 3, Line "Atelectasis", the data of (3 (2.4%)) is incorrect. It should be revised to (3 (7.3%)).

Reply 18: Thank you for your suggestion. We have corrected the data in the table 3.

## **Reviewer B**

Comment 1: Method - Follow up –

Please add more detailed information about the postoperative follow-up strategy in both groups.

Reply 1: Thank you for the useful suggestion. We have added the follow-up data in the revision. Follow-up data were obtained from telephone calls, or direct outpatient examinations. Patients were recommended to repeat CT and pulmonary function test at the 1, 3, 6,12 months during the first 2 years after operations. During each follow up session, information regarding patients' survival, cancer recurrence or metastasis, and cause of death was collected. In present study, the endpoint of follow-up was March 2019.

Change in the text: The revised part can be found in line 134 to 142 of the track changes version.

Comment 2: As for pathological stage, staged bilateral operation group had more advanced cancer (stage  $\geq 2$ ) (simultaneous vs staged: 24% vs 36%). Please consider the impact of this result on the prognosis.

Reply 2: Thank you for the helpful comment. The main reason that the stage II patients in the staging operation group is less than the patients with the simultaneous group is that some patients in the stage operation have tumor progression in the interval between operations, which makes the number of stage IA patients in the stage operation group

less than the simultaneous group. We therefore speculate that staged surgery may lead to the risk of tumor progression, which may affect the survival of patients.

Comment 3: Please add information about performing adjuvant chemotherapy.

Reply 3: Thank you for your suggestions. The adjuvant chemotherapy data could not be collected. We have added it in our limitation.

Change in the text: The revised part can be found in line 312 to 314 of the track changes version.

Comment 4: In this study, both groups included relatively young patients. Please discuss that the patients' age may influence the lower rate of their postoperative complications than previous reports.

Reply 4: Thank you for your suggestion. In the present study, we have analysis the influence of the patients' age in the table 3, we found that there was no significant difference in the postoperative complications between the simultaneous and staged operation.

Comment 5: Please add the ranges of the age, and spirometry result in table.

Reply 5: Thank you for the useful suggestion. We have added the range of the age and spirometry in table 1.

Change in the text: The revised part can be found in table 1 of the track changes version.

## **Reviewer C**

Comment 1: I suggest that the abstract (and the entire manuscript) contain both absolute numbers and percentages to allow easier comparisons.

Reply 1: Thank you for the useful suggestion. We had added the range of the age and spirometry in table1.

Change in the text: The revised part can be found in table 1 of the track changes version.

Comment 2: The description in the methods section of how the extent of resection was chosen was confusing. For example, it seems that a sublobar resection was used for solid tumors less than 2 cm in size. If that is true, I would that paragraph to clearly state that, and to present the criteria in such a way to cover all possibilities.

Reply 2: Thank you for your comment. We are deeply sorry for the confusion caused by this sentence. In this study, there were no patients underwent sub-lobectomy. the method that limited resection was the first choice for peripheral, ground glass opacity (GGO) dominant tumors with a size less than 2 cm, and for patients with high cardiopulmonary risk just was our surgical principles to preserve pulmonary function. In order to avoid ambiguity, we have deleted this sentence.

Change in the text: The revised part can be found in line 109 to 112 of the track changes version.

Comment 3: For the criteria where the predicted postoperative FEV1 of less than 1L excluded patients from surgery, please clarify if that was the predicted value after the considered bilateral resections. And please clarify how patients who would have tolerated a unilateral resection but not a bilateral resection were managed. For example, did you radiate the smaller tumor and resect the larger one?

Reply 3: Thank you for the useful comment. In this study, we used the total number of pulmonary segments that can be safely removed to predicted postoperative FEV1. This could also be used to predict postoperative pulmonary function as described by Zeiher. For example, right lower lobectomy with left lobectomy was the least common surgical type in the simultaneous resection. The right lower lobe is the largest lobe and accounts for about 25% of total pulmonary function. Therefore, right lower lobectomy with left lobectomy causes a considerable decline in pulmonary function. Simultaneous bilateral lobectomy should be considered carefully for those patients.

Comment 4: Please clarify the statement "for simultaneous resection, the procedure started at the relatively simple side" - how is/was "simple" defined?

Reply 4: Thank you for the useful comment. We have changed the sentence as “for

simultaneous resection, the procedure started at the side whose pulmonary function loss were less after resection”.

Change in the text: The revised part can be found in line 122 to 124 of the track changes version.

Comment 5: Most importantly, how did you decide who had simultaneous and who had staged surgeries? You don't seem to consider a selection bias, where you maybe chose healthier (and younger) patients for simultaneous procedures, which is why they lived longer.

Reply 5: Thank you for the useful comment. In this pilot study stage, the selection of simultaneous surgeries was mostly relied on surgeons' judgement. We have added it in our limitation. However, we showed that simultaneous resection had a significantly better OS than staged resection for those patients with bilateral pure solid nodules or tumor size > 3 cm. Simultaneous bilateral VATS lobectomy was considered as an alternative method for the treatment of SPLC.

Change in the text: The revised part can be found in line 311 to 313 of the track changes version.

Comment 6: Please clarify the surveillance methods (how and how often were people seen post-surgery).

Reply 6: Thank you for the useful comment. We have added the follow-up data in the revision. Follow-up data were obtained from telephone calls, or direct outpatient examinations. Patients were recommended to repeat CT and pulmonary function test at the 1, 3, 6,12 months during the first 2 years after operations. During each follow up session, information regarding patients' survival, cancer recurrence or metastasis, and cause of death was collected. In present study, the endpoint of follow-up was March 2019.

Change in the text: The revised part can be found in line 133 to 142 of the track changes version.

Comment 7: Were there any cross-overs, where patients were planned to get simultaneous surgery, that was converted to staged based on intra-operative events?

Reply 7: Thank you for your question. In our study, there were no patients converted to staged based on intra-operative events.

Comment 8: A cox model is needed to evaluate survival for the entire group. At the least, age, stage, co-morbidities as well as simultaneous versus staged must be considered. Otherwise, the conclusion that simultaneous procedures "preventing tumor progression compare to staged resection" is not supported and must be removed/toned down.

Reply 8: Thank you for the useful suggestion. We had performed a univariate and multivariate Cox regression analysis of overall survival after bilateral VATS lobectomy for SPLC in the table 5. In addition, subgroup analysis revealed that simultaneous resection had a significantly better OS than staged resection when bilateral tumors were pure solid ( $p=0.024$ ), or when the biggest tumor size was more than 3 cm ( $p=0.009$ ).

Comment 9: Please statistically compare the stage distributions between the 2 groups.

Reply 9: Thank you for the useful suggestion. We had made comparison of the stage distributions between the 2 groups in the table 2.

Comment 10: Why were post-operative stays so long? 13 and 16 days seems remarkable extended.

Reply 10: There was the total hospital stays, including pre-operative stays. And the staged surgery had double pre-operative stays.

Comment 11: Table 5 presents a regression analysis, but the methods do not mention this. Please clarify what was done exactly. Was logistic regression, or a Cox model? In addition, the survival analysis (see comment above) must consider the entire cohort.

In table 1, the % for size of the largest tumor adds up to 110 (not 100).

Reply 11: Thank you for your suggestion. In this study, a univariate analysis was

performed by a Fisher exact test or unpaired t-test to compare two factors. A multivariate analysis was performed by a logistic regression analysis using SPSS Statistics 21 (IBM, United States). And the percentage for size of the largest tumor has been changed.

Change in the text: The revised part can be found in line 149 to 150 of the track changes version.

Comment 12: Can the authors clarify how their data/results can be used to support who should get a simultaneous and who should get staged surgeries? That was the stated goal, but I don't see how the study helps with that question.

Reply 12: Thank you for your suggestion. In this pilot study stage, the selection of simultaneous surgeries was mostly relied on surgeons' judgement. We have added it in our limitation. However, we showed that simultaneous resection had a significantly better OS than staged resection for those patients with bilateral pure solid nodules or tumor size > 3 cm. Simultaneous bilateral VATS lobectomy was considered as an alternative method for the treatment of SPLC.