

Peer Review File

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Reviewer A

Comment: Very interesting work about the study of locoregional recurrence between trisegmentectomy of the left upper lobe versus lobectomy. The table shows the data referring to the T factor that includes data in relation to size. Although there are few patients in stage T2, it would be interesting to know the size of the tumor, since as they are candidates for performing a trisegmentectomy, their size will possibly be small and the stage will be conditioned by the invasion of the visceral pleura, which, in turn, may have prognostic implications.

Although this is a retrospective study on N0 patients, a reflection on N1 lymph node involvement in the intrapulmonary nodes is lacking when planning trisegmentectomies in the future. In short, a very interesting job.

Reply: Thank you very much for your positive comments. As you pointed out, we tended to perform segmentectomy for small tumors, although there were no significant differences based on pI factor. We attempted to minimize selection bias by using the clinical T factor as a covariate for propensity-score matching. As balance in terms of pathological stage is also important, we have included this information as well.

In this study, we only analyzed data of patients with cN0 tumors as cN1 or cN2 tumors are generally resected via lobectomy. However, we aim to analyze data on cN1 tumors in the intrapulmonary nodes in a future research study. Changes made to the text are as follows:

Page 14, Lines 5-7: Although not included in the propensity score matching procedure, the median consolidation size on CT was greater in the lobectomy group than in the trisegmentectomy group (25.0 mm vs. 14.5 mm, $p < 0.001$).

Page 14, Lines 10-11: The median consolidation size on the CT image was also similar in both groups.

Page 15, Lines 6-7: In terms of postoperative oncological outcomes, the pI factor and pathological stage were similar between groups (Table 2).

Reviewer B

Comment 1: The concept of the paper is interesting, but are the numbers large enough to show a difference if there is one (is it adequately powered)?

Reply 1: Thank you for raising this important concern. We agree that the sample size was relatively small, which might have influenced the statistical power of the analysis. Accordingly, we have cited this as a limitation of the study in the revised Manuscript. Changes made to the text are as follows:

Page 19, Line 16 to Page 20, Line 1: Second, the number of patients was relatively small. The current study should be considered preliminary based on the sample size.

Comment2: Second, the distance from the intersegmental plane is of importance if a close margin is inappropriate. For many of your nodules close to the plane, if the distance was still equal to the size of the tumor, it would be fine. Do you have those numbers available?

Returning to the first point, if there were only a few patients with tumors larger than the margin to the intersegmental plane, you can't prove your point. Then. this is a repeat of prior papers comparing trisegmentectomy to left upper lobectomy.

Reply 2: Thank you for your comment. The pathological distance from the intersegmental plane was not measured for many specimens. Instead, if the nearest surgical margin seemed close to the tumor, the negative surgical margin was confirmed using intraoperative stump cytology.

Reviewer C

Comment: Thank you for allowing me to review the manuscript entitled “An equivalent oncological clearance of trisegmentectomy to lobectomy in left upper division in non-small-cell lung cancer” by Nishikubo et al. The authors investigated 252 patients with lymph node-negative NSCLC who underwent either left apical trisegmentectomy or left upper lobectomy. After propensity-score matching, 46 pairs of patients were created which were further analyzed. Furthermore, they performed a further analysis of the patient cohort depending on the distance of the lung tumour from the intersegmental plane between the left upper division and lingula. This subgroup analysis might be potentially interesting. However, the sample size is relatively small to conclude.

Reply: Thank you for raising this important concern. We agree that the sample size was relatively small, which might have influenced the statistical power of the analysis. Accordingly, we have cited this as a limitation of the study in the revised manuscript. Changes made to the text are as follows:

Page 19, Line 16 to Page 20, Line 1: Second, the number of patients was relatively small. The current study should be considered preliminary based on the sample size.

Major points

Comment 1

Study population: It is stated that N0 NSCLC patients were included. Which clinical or pathological stages were included?

Reply 1: Thank you for your relevant question. We retrospectively analyzed data of patients with cN0 non-small-cell lung cancer in the left upper division who underwent left upper lobectomy or trisegmentectomy. (Page 3, Lines 11-12; Page 8, Lines 12-14).

Comment 2

2) Page 8, Line 10: `Patients with missing values were excluded from the analyses. Please specify the values

Reply 2: Thank you for your comment. In accordance with your suggestion, we have revised the text as follows to address this issue:

Page 13, Line 15 to Page 14, Line 1: Seventeen patients were excluded because of missing values (15 who did not undergo positron emission tomography CT, 2 without preoperative FEV1.0/FVC data, and 1 who underwent completion lobectomy due to lingula torsion after trisegmentectomy).

Comment 3

3) Page 9, Line 10: `systemic injection of indocyanine green` Did every patient in this study (beginning in 2006) receive ICG during the operation? Please specify

Reply 3: Thank you for this relevant question. The inflation–deflation line technique was used initially, and since 2018, ICG technique has been used with or without the inflation-deflation method. To address this issue, we have revised the text as follows:

Page 9, Line 16 to Page 10, Line 2: The jet ventilation technique was used to identify the demarcation line using the inflation–deflation line as a reference (13); however, since 2018, systemic injections of indocyanine green (0.3 mg/kg) were used with or without the inflation-deflation method (14).

Comment 4

**4) Page 10, Line 10: `head magnetic resonance imaging and bone scintigrams`
Could you please respond if every N0 NSCLC patient receives this kind of follow-up postoperatively?**

Reply 4: Thank you for your comment. In our institution, almost all patients with NSCLC undergo postoperative follow-up involving head magnetic resonance imaging and bone scintigraphy.

Comment 5

5) The statistical analysis section needs to be improved

Reply 5: In accordance with your comment, we have heavily revised the statistical analysis section for language and grammar.

Comment 6

6) Page 13, Line 6: hospital stay of 16 days vs. 13 days. Would that be the mean or the median? In any case, could you please comment on this result? How many patients were operated through VATS, and how many through thoracotomy?

Reply 6: Thank you for raising these important concerns. Mann–Whitney U-tests were used to compare continuous variables in this study; therefore, the values are presented as the median. This detail is now included in the Results section and in Table 2. We have also added the proportion of patients who underwent VATS in Table 2. Changes made to the text are as follows:

Page 14, Line 14-17: Although the median operation time was shorter in the L group than in the S group (162 min vs. 181 min, $p=0.03$), there were no significant differences in median blood loss (85 mL vs. 90 mL, $p=0.19$), median hospital stay (16 days vs. 13 days, $p=0.06$), or morbidity rate (15.2% vs. 6.5%, $p=0.32$) between the matched cohorts.

Comment 7

7) Page 13, Line 10: `prolonged air leakage or delayed air leakage` could you please define these 2

Reply 7: Thank you for your comment. We have included the definitions for “prolonged air leakage” and “delayed air leakage” in the revised manuscript as follows:

Page 10, Line 16 to Page 11, Line 2: Prolonged air leakage was defined as air leakage lasting for >7 days or necessitating pleurodesis or invasive procedures (surgery or additional tube thoracostomy). Delayed air leakage was defined as air leakage necessitating tube thoracostomy after discharge.

Comment 8

8) I highly recommend thoroughly checking the whole manuscript for grammar and typos. On some occasions, I would consider changing the chosen word to help make the text clearer

i.e. Page 3, Line 7: interlobular with interlobar

Page 3, Line 15: consider replacing `certificate`

Page 4, Line 13: `even though`, consider replacing it with even if

Reply 8: In accordance with your comments, the manuscript has undergone a thorough professional language review by a native speaker of English with expertise in the subject matter. The issues above as well as the remaining grammatical and usage issues have been addressed during preparation for resubmission.

Page 3, Line 5-7: Although bilobectomy is not recommended for right upper or middle lobe tumors close to the interlobar plane, lobectomy is often performed for tumors located close to the intersegmental plane in the left upper division.

Page 3, Line 13-16: To verify whether trisegmentectomy was indicated regardless of tumor distance from the intersegmental plane, we compared recurrence-free survival rates following trisegmentectomy between patients with tumors ≤ 20 mm and >20 mm from the intersegmental plane.

Page 4, Line 9-12: Our analysis suggests that oncological outcomes (i.e., recurrence-free survival rates) following trisegmentectomy for cN0 non-small cell lung cancer in the left upper division are not significantly inferior to those following lobectomy, even if the tumor is located close to the intersegmental plane.

Reviewer D

Major points

Comment 1

It is impossible to discuss the validity of some surgical procedure by comparing only about 40 cases treated with it with about 40 cases treated with standard operation.

It is clinically meaningless to divide the few 40 cases further into two groups and compare them.

Reply 1: Thank you for raising this important concern. We agree that the sample size was relatively small, which might have influenced the statistical power of the analysis. Accordingly, we have cited this as a limitation of the study in the revised manuscript. Changes made to the text are as follows:

Page 19, Line 16 to Page 20, Line 1: Second, the number of patients was relatively small. The current study should be considered preliminary based on the sample size.

Minor points

Comment 2

Title should be changed. The expression “trisegmentomy to lobectomy in left upper division” is strange. The expression, “oncological clearance” should also be changed.

Reply 2: Thank you for your comments. In accordance with your suggestions, we have revised the title as follows: Comparison of oncological outcomes between trisegmentectomy and lobectomy for non-small cell lung cancer in the left upper division. (*Page 1, Lines 1-2*).

Comment 3

P3 Line 5 “This division” is strange

Reply 3: In accordance with your comments, the text has been revised as follows:

Page 3, Lines 4-5: This anatomical classification is similar that used for the right upper and middle lobes.

Comment 4

P3 Line 6 The expression “a right upper or middle tumor” is strange

Reply 4: In accordance with your comments, the text has been revised as follows:

Page 3, Lines 5-7: Although bilobectomy is not recommended for right upper or middle lobe tumors close to the interlobar plane, lobectomy is often performed for tumors located close to the intersegmental plane in the left upper division.

Comment 5

P3 Line 9-10 The expression “whether oncological outcomes depend on the tumor’s location” should be changed.

Reply 5: In accordance with your comments, the text has been revised as follows:

Page 3, Lines 7-9: To aid in establishing trisegmentectomy as a standard treatment for cN0 non-small cell lung cancer in the left upper lobe, we aimed to re-assess its feasibility based on oncological outcomes according to tumor location.

Comment 6

P3 Line 15 The expression “between each group” is strange

Reply 6: In accordance with your comments, the text has been revised as follows:

Page 3, Lines 12-13: After propensity score matching, oncological outcomes were compared between the trisegmentectomy and lobectomy groups.

Comment 7

P4 Line 1-2 Which group was the tumor with 20mm distance from the intersegmental plane stratified in?

Reply 7: Thank you for this relevant question. The original text did not indicate the stratification for tumors located 20 mm from the intersegmental plane. Therefore, the text has been revised to indicate that these tumors were included in the short-distance group. Relevant revisions to the groupings have been made throughout the manuscript.

Comment 8

P4 Line 5 The expression “the 5-year RFS between lobectomy and segmentectomy” is strange.

Reply 8: In accordance with your comments, the text has been revised as follows:

Page 4, Lines 1-3: There was no significant difference in the 5-year recurrence-free survival rate between the lobectomy and trisegmentectomy groups (75.5% vs. 84.0%, $p=0.41$).

Comment 9

P4 Line 9 The expression “the tumor distance was nonsignificant” is strange.

Reply 9: In accordance with your comments, the text has been revised as follows:

Page 4, Lines 6-8: Multivariate analysis indicated that tumor distance from the intersegmental plane was not a significant predictor of recurrence-free survival (hazard ratio: 1.75, 95% confidence interval: 0.52–5.91, $p=0.37$).

Comment 10

P6 Line 3 The expression “Segmentectomy is increasingly popular” is strange.

Reply 10: In accordance with your comments, the text has been revised as follows:

Page 6, Lines 2-4: Segmentectomy has become increasingly popular for the resection of early-stage non-small cell lung cancer (NSCLC) given its ability to preserve pulmonary function compared with lobectomy (1-3).

Comment 11

P6 Line 13 The expression “This division” is strange.

Reply 11: In accordance with your comments, the text has been revised as follows:

Page 6, Lines 15-16: This anatomical classification is similar to that used to classify the right upper and middle lobes.

Comment 12

P8 Line 4 “All participants provided written informed consent before enrolment. “ Is this true?

Reply 12: Thank you for this relevant question. This retrospective study was conducted and analyzed in 2019. However, our institution had obtained general written informed consent from all the patients regarding the research use of their information. In addition, on October 25 2019, IRB approved this retrospective study on the condition that ‘opt-out’ consent approach on the website had been carried out as an alternative to informed consent from each patient.

Comment 13

P8 Line 19 The expression “Patients with missing values” is strange.

Reply 13: In accordance with your comments, the text has been revised as follows:

Page 8, Lines 16-17: Patients with missing data for specific values were excluded from the analyses.

Comment 14

P10 The expression “distant recurrence was defined as recurrence in the contralateral lobes or lymph nodes outside the hemithoracic organs or dissemination in the pleural space “ is strange.

Reply 14: In accordance with your comments, the text has been revised as follows:

Page 11, Lines 7-8: ...while distant recurrence was defined as recurrence in the contralateral lobes, in lymph nodes outside the hemithoracic organs, or as dissemination in the pleural space.

Comment 15

P10 Line 14 The expression “To expand the indication of trisegmentectomy for tumors in the left upper division independently of the distance from the intersegmental margin, we performed the following analysis” is strange.

Reply 15: In accordance with your comments, the text has been revised as follows:

Page 12, Lines 5-7: To determine whether the indication for trisegmentectomy can be expanded to tumors in the left upper division regardless of distance from the intersegmental margin, we performed the following analyses (Figure 1).

Comment 16

P11 Line 5-6 The expression “we compared the recurrence-free survival (RFS) between the cases” is strange.

Reply 16: In accordance with your comments, the text has been revised as follows:

Page 12, Lines 12-15: To verify whether trisegmentectomy was indicated independently of the tumor’s location, we compared RFS between patients undergoing trisegmentectomy for tumors located ≤ 20 mm from the intersegmental plane and those located >20 mm from the intersegmental plane.

Comment 17

P11 Line 8 The expression “ox proportional hazards model were” is strange.

Reply 17: In accordance with your comments, the text has been revised as follows:

Page 12, Line 15-17: A multivariate Cox proportional hazards model was used to identify predictors of RFS in the trisegmentectomy group. Age, distance from the intersegmental plane, and SUVmax were used as covariates.

Comment 18

P12 The expression “15 did not perform PET-CT, two were not measured pre-operative FEV1.0%” is strange.

Reply 18: In accordance with your comments, the text has been revised as follows:

Page 13, Line 15 to Page 14, Line 1:

Seventeen patients were excluded because of missing values (15 who did not undergo positron emission tomography CT, 2 without preoperative FEV1.0/FVC data, and 1 who underwent completion lobectomy due to lingula torsion after trisegmentectomy).

Comment 19

P12 Line 13-4 The expression “The proportion of the patients with SUVmax >2.5 was higher in lobectomy than trisegmentectomy (68.9% vs. 46.8%, p=0.002). “ is strange.

Reply 19: In accordance with your comments, the text has been revised as follows:

Page 14, Lines 3-5: The proportion of patients with an SUVmax of >2.5 was higher in the lobectomy group than in the trisegmentectomy group (68.9% vs. 46.8%, p=0.002).

Comment 20

P13 Line 2-3 The expression “Demographic and oncological characteristics of the patients are shown in Table 1, which confirms the equality between the two groups. “ is strange.

Reply 20: In accordance with your comments, the text has been revised as follows:

Page 14, Lines 9-10: The demographic and oncological characteristics of the patients are shown in Table 1, which shows the similarities between the two groups.

Comment 21

P14 Line 15-6 Why did you do univariate analysis multivariate analysis after multivariate analysis?

Reply 21: Thank you for your relevant question. Several post hoc sensitivity analyses were performed to verify our findings. First, RFS was compared between the unmatched lobectomy and trisegmentectomy groups. Second, univariate analysis of RFS was performed in the trisegmentectomy group without adjusting for other covariates. However, if these analyses are deemed unnecessary, we will remove them from the manuscript. This explanation is now included in the revised manuscript (*Page 13, Lines 1-4*). The other relevant changes made to the text are as follows:

Page 17, Lines 1-2: Univariate sensitivity analysis yielded similar findings (hazard ratio: 0.79, 95% confidence interval: 0.24–2.56, $p=0.69$).

Comment 22

P15 Line 8-9 You should clarify the source of references.

Reply 22: Thank you for your comment. We have added references for CALGB140503 to the manuscript. The citation for JCOG1211 has been deleted because the results have not been presented yet.

Page 17, Lines 5-7: Although multi-institutional randomized clinical trials (JCOG0802/WJOG4607L and CALGB140503) have demonstrated the clinical value of segmentectomy, these trials were limited to patients with peripheral small-sized NSCLC (4,15).

Reviewer E

Comment 1:

1) The authors should describe how extent of lymph node (LN) dissection was performed in tri-segmentectomy and lobectomy. When any LNs (#13, #12, #11) dissected had been diagnosed as metastasis intraoperatively, was the surgical procedure converted from segmentectomy to lobectomy or not? In addition, please explain how the patients who underwent segmentectomy were treated when LN metastasis had been confirmed postoperatively.

Reply 1: Thank you for these relevant questions and comments. As noted in the revised manuscript, patients undergoing segmentectomy or lobectomy for cN0 NSCLC at our institution also generally undergo selective mediastinal lymphadenectomy. When a positive hilar lymph node is suspected based on intraoperative visualization, pathological node assessments are performed using frozen sections. When findings from frozen sections are positive, the procedure is converted from segmentectomy to lobectomy. Regarding the second part your comment, even when histopathological examination revealed lymph node metastasis, specific treatments were not performed, and adjuvant chemotherapy was incorporated according to usual indications. This description is now included in the revised manuscript (*Page 10, Lines 5-10*).

Comment 2

2) I would recommend that this study would include pathological data such as pTNM. In addition, p-Stage should be applied in propensity score matching

Reply 2: Thank you for your comment. The clinical T factor was included as a covariate for propensity score matching to reduce selection bias related to surgical procedures. However, as balance in terms of pathological stage is also important, we have included this information in accordance with your suggestion. Changes made to the text are as follows:

Page 15, Lines 6-7:

In terms of postoperative oncological outcomes, the pI factor and pathological stage were similar between groups (Table 2).

Comment 3

3) The authors should show postoperative respiratory function. A comparison of the reduction in EFV1 or VC between two groups will be of much interest to the readers of the journal.

Reply 3: Thank you for your comment. We agree that postoperative respiratory function is also an important consideration for this population. Accordingly, we analyzed the change rate of FEV1.0 from the preoperative assessment to the postoperative assessment at 6 months. Changes made to the text are as follows:

Page 11, Lines 2-4: The change rate of forced expiratory volume in 1 s (FEV1.0) was defined as the change between preoperative and 6-month postoperative measurements.

Page 15, Lines 4-6: The change rate of FEV1.0 tended to be higher in the S group than in the L group, although the difference was not significant (88 % vs. 90 %, p=0.29).

Comment 4

4) In the Method (P3, line11), the authors should define the recurrence-free survival (RFS). Generally, RFS is defined as the period from the date of surgery to recurrence or death from any cause. It would be better if the data of overall survival (OS) was included in this study.

Reply 4: Thank you for your pertinent comments. In accordance with your suggestion, we have included definitions for RFS and OS in the Methods section. We have also included OS data in the Results section and in Figures 3 and 4. Changes to the text are as follows:

Page 11, Lines 8-10: Recurrence-free survival (RFS) was defined as the period from the date of surgery to recurrence or death from any cause. OS was defined as the period from the date of surgery to death from any cause.

Page 15, Line 16 to Page 16, Line 1: The 5-year OS rate did not significantly differ between the groups (82.0% vs. 83.3%, $p=0.93$, Figure 3B).

Page 16, Line 16 to Page 17, Line 1: The 5-year OS rate did not significantly differ between the short- and long-distance groups (79.0% vs. 80.2%, $p=0.63$, Figure 4B).

Comment 5

5) I believe that data of surgical margin distances of the resected lung besides preoperative radiological distances provided in this study are necessary to address oncological outcomes according to resection margin. From these results, a comparison between the actual and virtual distances might lead to validity of the authors' hypothesis.

Reply 5: Thank you for your comment. The pathological distance from the intersegmental plane was not measured for many specimens. Instead, if the nearest surgical margin seemed close to the tumor, the negative surgical margin was confirmed using intraoperative stump cytology.

Comment 6

6) One of major concerns is the statistical analysis of a Cox proportional model for RFS. To contain five variables in a Cox proportional hazard model, events (recurrence and death) of fifty (5 times 10) is needed. In the manuscript (P14, line9-12). However, total number (event) of recurrences in segmentectomy is six, which would be insufficient, although the number of deaths is not described.

Reply 6: Thank you for raising this important concern. We agree that the number of variables used in the Cox proportional model for RFS was inappropriate. Therefore, we eliminated sex and presence of GGOs, leaving three variables in the analysis of RFS. The relevant changes made to the text are as follows:

Page 4, Lines 6-8: Multivariate analysis indicated that tumor distance from the intersegmental plane was not a significant predictor of recurrence-free survival (hazard ratio: 1.75, 95% confidence interval: 0.52–5.91, $p=0.37$).

Page 12, Lines 16-17: Age, distance from the intersegmental plane, and SUVmax were used as covariates.

Page 16, Lines 14-16: Multivariate analysis revealed that the distance from the intersegmental plane was not a significant predictor of RFS (hazard ratio: 1.75, 95% confidence interval: 0.52–5.91, $p=0.37$, Table 3).