Peer Review File
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Reviewer A

We would like to congratulate the authors on their manuscript entitled: “mediastinal lymph node evaluation, especially at station 4L in left upper lobe lung cancer. Please find the comments below.
Reply: Thank you very much for the insightful comments. Below, we have responded to all of the reviewers’ queries in a pointwise manner.

Overall comments
- Refrain from the use of non-common abbreviations as these trouble reading, including LN, LND, DFS, OS, RLNP and so on.
Reply: Except for the commonly used abbreviation LN, we refrained from using any other common abbreviations in the text.

Introduction
- Please be more specific in your research question at the end of the section.
Reply: We have corrected the last paragraph of the Introduction to clarify our research question (Page 8, Lines 96-99).
- Add reference to the STROBE guidelines
Reply: We have added the corresponding reference for the STROBE guidelines (Page 8, Line 98).

Methods
- Line 98, remove “=”
Reply: We have removed “=.”
- Add the approval date of the study
Reply: We have added the approval date to the revised text (Page 9, Line 105).
- Did all patients present with NSCLC?
Reply: All but four cases were those of NSCLC. Three cases were of stage 1 disease, while histological diagnosis was confirmed for the other one during the operation.
- What is considered as a video recording of sufficient quality? Isn’t the thoracoscopic view recorded? If it is of insufficient quality how could the surgery then be adequately performed? In addition, for the discussion part. Was there an association between a surgery wherein the video was considered of insufficient quality and complications?
Reply: Video-assisted thoracoscopic surgery is worth evaluating as all surgical procedures are recorded on the video. However, in open thoracotomy with hybrid VATS, cases with missing records of dissection procedures were excluded because they were inappropriate for evaluation. Therefore, there was no correlation between the video quality and surgical complications.

- Line 157 belongs in the results section.
Reply: We did not have a suitable place to move "The median follow-up period was 44 (range, 0–137) months." in the Results, because of which we have retained it. If you can indicate the appropriate place to move it, we can respond accordingly (Page 12, Line 170).
- Statistical analyses: denote how continuous variables etc were denoted. How was normality tested?
Reply: All of our analyses in this study are comparisons between two groups using nominal variables.

Results
- Would it also be interesting to state the NNT for mediastinoscopy versus no mediastinoscopy in the light of N2
Reply: Thank you for the interesting suggestions. However, unfortunately, we excluded cases that underwent preoperative induction therapy, and thus, it was not meaningful to consider NNT for mediastinoscopy versus no mediastinoscopy in the light of N2. One reason is that not all excluded cases were pathologically confirmed preoperatively. Another reason is that mediastinoscopy cannot evaluate stations 5LN and 6LN, and so, the accurate positivity rate of pN2 cannot be calculated. We were also interested in the comparison with VAMLA, although we would like to consider a study in combination with the evaluation methods of stations 5LN and 6LN in the future.
- Discussing why station 4L was not identified as prognostic factor belongs in the discussion section.
Reply: "One reason may be the exclusion of node-positive patients at station 4L on mediastinoscopy. Another reason may be that only node-positive patients were pathologically evaluated, and LN status without resection for pathological examination was not considered." has been moved to the Discussion (Page 17, Lines 261-263).
- It is not allowed to state that 0.10 is “more significant” than 0.35, since both are just “not significant”, as also stated in the methods section. It was not exactly stated like this, however, distilled from lines 187-189 and above.
Reply: Thank you for the helpful suggestion. The part that was pointed out has been changed as follows: “Intraoperative videos were used to confirm whether LNs were evaluated at the undissected station; however, no significant difference was observed in disease-free survival, thus suggesting that no method was superior for dissection to evaluate metastatic LNs.” (Page 18, Lines 265-267).

- Stratify RLNP based on temporary and permanent. And if you do so, please provide a proper definition in the methods section. Words as mild RLNP are highly subjective.
Reply: We deleted “mild RLNP” because it is an ambiguous expression.

Discussion
- Part of patients had prior mediastinoscopy evaluating station 4L, making the prior

chance on unforeseen N2 disease or micrometastases in this station less expected, should we still evaluate this station after negative mediastinoscopy? Please comment on this.
Reply: As mentioned in the second paragraph of the Discussion, there is a possibility that station 4L has not been fully evaluated for the following reasons: one is that station 4L has an unexpectedly wide dissection area. The other is passive sampling to avoid paralysis or bleeding due to the procedure near the running of the recurrent nerve. We think the important point is whether to focus on the onset of complications or the detection of upstaging cases of about 4%. We believe that it is important to accurately stage lung cancer with a poor prognosis and to provide postoperative adjuvant treatment for advanced cancer cases.
- Please discuss on the use of VAMLA to resect station 4L, also given its supposed increased accuracy compared to video-assisted mediastinoscopy, especially considering the decrease in unforeseen pN2. (see e.g., Lozekoot, Pieter WJ, et al. "Surgical mediastinal lymph node staging for non-small-cell lung carcinoma." Translational Lung Cancer Research 10.8 (2021): 3645.)
Reply: We have discussed VAMLA's utility in the Discussion as follows: "Video-assisted mediastinoscopic lymphadenectomy (36) not only allows bilateral mediastinal LN evaluation but also demonstrates superior sensitivity and negative predictive value relative to the currently prevalent endobronchial ultrasonography." (Page 20, Lines 303-305).

Conclusion
- Your conclusions are not all backed by hard value-based evidence coming from the article's body. Please adapt.
Reply: Accordingly, we have revised the conclusions based on the evidence in the main article (Page 21, Lines 317-322).

Reviewer B

Proper and accurate lymphadenectomy in patients with NSCLC is a key element of surgical treatment, allowing, above all, for precise staging and qualification of the patient for further oncological treatment. Despite the new trend promoting limited resection of the mediastinal lymph nodes, the majority of the thoracic surgeon community still recomondes LND, not LNS. In the case of left-sided lung cancer resections, the 4L station is re-resected relatively rarely. This is mainly due to the specific anatomical conditions of this mediastinal region and the risk of laryngeal recurrent nerve paresis. In the presented matrix, the discussed complication occurred in 20 (14.39%) patients, of which 15% required surgical intervention. Metastases to the 4L station were found in 6.47% of the respondents. Interestingly, in 1/3 of 4L-positive cases, mediastinoscopy was performed, which showed no metastases. The paper does not show whether all patients qualified for the surgery had PET-CT

examination, which may explain the high percentage of patients with positive 4L who did not undergo mediastinoscopy (6/9 patients). The use of video recording for the assessment by independent experts of the technique of 4L lymph node removal seems to be an interesting procedure. As shown by the authors, one of the most important risk factors was the use of devices such as the electric knife and vessel sealing system. What is important, in the one-variant analysis, a higher percentage of RLNP was demonstrated in patients after thoracotomy, which may suggest that the above-mentioned devices were used in open section surgery. Daily practice rather indicates that various types of electrical devices are more often used in VATS-lobectomes. Unfortunately, the authors did not indicate whether there are procedures in place to reduce the risk of RLNP. Therefore, the question remains whether in the case of 4L station resection, the risk of complications outweighs the potential benefits of accurate lymphadenectomy, given that the risk of 4L nodal metastases is not high, and the presence of 4L metastases is not a porognostic factor. In the context of the work in question, it is difficult to draw such conclusions, given the retrospective nature of the work and the relatively small size of the study group. Nevertheless, the work indicates an important aspect of the issue discussed and in this aspect it has a practical value. Undoubtedly, the problem of RLNP should be the subject of further research.
Reply: Thank you very much for your invaluable insightful comments. A more accurate and minimally invasive assessment of the medial lymph node (LN) is important to determine the indications for further oncological treatment induction. Nevertheless, we agree with the reviewer that the risk benefits of performing station 4L LN dissection must be fully evaluated. If a case with a clearly low risk of metastasis to the medial LN is identified, dissection should not be performed to avoid complications such as RLNP.
However, since there are no clear predictors at this time, it is necessary to perform accurate LN dissection if there is any possibility of omission during evaluation. Therefore, we evaluated the relationship between the procedure that could cause RLNP and occurrence of RPNP using intraoperative videos. The important precautions for the LN dissection technique that we propose to avoid RNLP are reliable confirmation of running of recurrent nerve and its protective operation. Since it is difficult to evaluate a protective operation, we focused on the use of an electric cautery or a vessel sealing system in the vicinity of the recurrent nerve. Open thoracotomy is mainly indicated for advanced lung cancer, and thus, aggressive dissection using an electric cautery may have contributed to RLNP. The vessel sealing system is mostly used in VATS, and the safety of its usage has improved over time. FDG-PET was performed in 123 of 139 cases. Neither FDG-PET nor mediastinoscopy was performed in seven cases, whereby no case was positive for metastasis by 4L LN dissection from the thoracic cavity side.

Reviewer C

I congratulate the authors of this study, who have investigated the impact of lymph node dissection in left upper lobe lung cancer and have shown that the presence of N2 disease in patients with no previous histological evidence of N2 disease is associated with reduced survival. The link between N2 disease and poor survival is however already known, and therefore, the analysis of the importance of addressing station 4L and its associated link with complications and outcomes is the most important component of this well-written study.

The main issue I have is the need for a section at the start of the results to clearly outline the characteristics of these patients. The following needs to be included and summarised:
Total number of patients
Demographics: age, gender, maybe some comorbidity data
Open vs VATS approach
Number of patients who underwent LND, including stations 4L, 5 and 6
Incidence of metastatic lymph node disease
Number of patients who underwent mediastinoscopy
Number of patients with confirmed primary lung cancer prior to surgery
Inclusion of such data at the start would make the ensuing results section much easier to navigate.
Reply: Thank you for your recommendation.
We have created a new Table 1 to present the patients' characteristics and added the explanation at the beginning of the Results (Page 13, Line 182 - Line 193). It should be noted that some items were included in the existing Table 1, 2 3 and 4.

As this study excludes patients with known N2 disease, this study is in essence examining the rate of nodal upstaging in left-sided lung cancer. Therefore, it is very important to focus on staging methodology in this patient cohort. In the 'mediastinoscopy' subsection of the methods section, you need to outline clearly which patients underwent mediastinoscopy, and whether patients who underwent EBUS also underwent mediastinoscopy or not? Some extra data in the results section may also be useful here, including tumour size, suspicion of N1 disease and histology.
Reply: Thank you for the insightful suggestions. We have modified the content on Mediastinoscopy in the Methods to clarify its association with EBUS. In addition, tumor diameter, cN, and histology are described in the newly added Table 1 (Page 10, Lines 130-135).

The discussion section focusses clearly on the main themes in this area of lung cancer surgery and provides an excellent overview of RLNP. The statistical analysis is robust and the results clear. I think this paper will be a worthy addition to the literature if the above issues are addressed. I have a number of minor points which are outlined below.
Reply: Below, we provide systematic pointwise replies to each of the comments.

Line 49: ‘Pathological N stage ≥2 was an independent prognostic factor for disease-free survival (P=0.005).’ This sentence should be at the end of the results section of the abstract rather than the beginning.
Reply: The obtained results are listed in the order followed in the Results.
As instructed, we have moved this sentence to the end of the Results (Page 5, Lines 60-61).
Lines 64-65: “pulmonary lobectomy with lymph node (LN) dissection (LND) is necessary for the treatment of primary non-small cell lung cancer (NSCLC).” As you go on to mention, there is not yet unequivocal evidence stating that LND is necessary. Perhaps an alternative term, such as lymph node harvesting, so as to cover all methods including dissection and sampling, may be preferable.
Reply: We changed “lymph node dissection” to “lymph node harvesting”. (Page 7, Line 70).
Line 172. The brackets should state Table 1, not Figure 1.
Reply: Accordingly, we have changed “Figure 1” to “Table 2” (Page 14, Line 199). We apologize for the oversight.
Line 176: the % is wrong. You quote 8.57% but give a value of six out of nine patients (66.7%). Similar for line 177 with regards to the other three patients
Reply: As instructed, we have changed “8.57%” to “66.7%” and “4.35%” to “33.3” (Page 14, Lines 203 and 204).
Line 190: Should say Recurrent laryngeal nerve paresis
Reply: Accordingly, we changed “Laryngeal Recurrent Nerve Paresis” to “Recurrent laryngeal nerve paresis” (Page 15, Line 216).
Table 5: The middle column is out of sync with the surrounding columns
Reply: We have synced the middle column with the surrounding columns.

Reviewer D

I would like to congratulate the authors for their effort. It is a comprehensive review of surgical lymph node staging in left upper lobectomies and those possible factors that influence recurrent laryngeal nerve injury.

However, I would like to draw their attention to a few points:

-Lines 63-65 the authors state “Although other therapeutic options are available, pulmonary lobectomy with lymph node (LN) dissection (LND) is necessary for the treatment of primary non-small cell lung cancer (NSCLC)”. I do not believe this expression is the most appropriate, given that it may imply that treating lung cancer should be always mandatory, usually subject to subjective criteria by the patient and certain conditions of operability and resectability. I think it would be better to say that surgery continues to be the best therapeutic tool for the treatment of lung cancer (or another similar expression preferred by the authors).

Reply: Thank you for the kind suggestions. The sentence you have pointed out has been changed to “Despite the availability of treatment options, pulmonary resection with lymph node (LN) harvesting remains the best therapeutic tool for the treatment of primary non-small cell lung cancer (NSCLC)." (Page 7, Lines 69-71).

-Lines 116-117 the authors state “Preoperatively, the LN was considered positive if its short axis was >1cm on contrasted-enhanced computed tomography (CT)”. I think it is more correct to say that the LN was considered suspicious rather than positive. Likewise, I do not know if the authors would also consider a hyperuptake adenopathy in PET-CT as suspicious regardless of its size…
Reply: The part you have pointed out has been changed. Regarding FDG-PET, according to the Japanese guidelines, even lymph nodes with FDG accumulation do not affect the staging. If there is a strong suspicion of lymph node metastasis, such as in the case of unilateral FDG accumulation regardless of the size, mediastinoscopy is actively performed (Page 10, Lines 123-124).

-Lines 125-128 the authors state “Mediastinoscopy was performed before lobectomy on the day of surgery. Specimens routinely biopsied from stations 2R, 2L, 4R, 4L, and 7 were rapidly confirmed intraoperatively for the presence of metastases. In the presence of metastases, lobectomy was discontinued, and neoadjuvant therapy was initiated”. I do not know if it is a usual attitude of the authors to rule out patients for surgery after the finding of an incidental N2 during surgery, but since stage IIIA-N2 is so heterogeneous, I do not know if perhaps the authors would consider surgery in selected cases of unistation N2? Especially if the patients in whom they perform mediastinoscopy are those cN0-1.
Reply: The response to pN2 was decided by our surgical team, not by individual judgment. In right lung cancer, mediastinal LN dissection is sufficiently performed for cases with single pN2, because of which adjuvant treatment was introduced postoperatively. Since this study design was limited to left upper lobe lung cancer, surgery by mediastinoscopy was discontinued if superior mediastinal LN metastasis was positive by sampling. This is because medial lymph node dissection could not be performed sufficiently even from the thoracic cavity side, and the same applied to cases of cN0-1.

-Line 151 the authors state “Blood tumor marker testing and chest/abdominal CT were routinely performed every 6 months…”. I do not know which tumor markers the authors are referring to as there is no marker that has been shown to be effective for the diagnosis or follow-up of patients with nsclc.
Reply: The tumor marker whose laboratory value was elevated preoperatively was used as an index. However, in some cases, the value of the tumor marker was not enhanced. In such cases, we measured CEA and SLX for adenocarcinoma, Cyfra21-1 and SCC for squamous cell carcinoma, and proGRP and NSE for neuroendocrine tumors, in the hope to trigger the detection of recurrence. All tumor markers have been added to the manuscript (Page 12, Line 162-163).

-Line 193 the authors state that open surgery behaved as a risk factor for recurrent nerve palsy. I would have liked the authors to have delved into this topic in the discussion by providing possible hypotheses.
Reply: The cases whereby open thoracotomy had to be selected were those of clearly advanced cancer as compared with VATS. In these cases, pN2 was found in 5 of 12 (41.7%) cases of open thoracotomy with recurrent laryngeal nerve palsy as well as locally advanced cancer. One possible reason could be that aggressive lymph node dissection was required. Another reason was that several cases with open thoracotomy employed electric cautery for lymph node dissection, and as mentioned in the Discussion section, it was likely that the burns from the device exerted an effect. In the multivariate analysis, open thoracotomy was not an independent risk factor; therefore, no particular consideration was given. If you prefer that we add this explanation to the Discussion section, we will oblige.

-Table 1. The authors distinguish between patients with bleeding >200 mL and <200 mL, as well as duration of surgery >300 min or <300 min. Is there any reason to establish such specific cut-off points? Is it so common for a lobectomy to last more than 5 hours?
Reply: The average result of the operation for lung cancer, including open thoracotomy and VATS, in an institution with a respiratory surgeon, is that the blood loss is up to approximately 200 milliliters during bleeding and the operation duration is 2 to 4 h in Japan. Therefore, the cut-off values for the amount of blood loss and length of the operation duration were set to 200 mL and 300 min, respectively, although there was no clear basis. In fact, we analyzed the values at 100, 200, and 300 mL of blood loss and at 3, 4, and 5 h of operation duration; however, no significant differences were found. Therefore, the results of only typical cut-off values are shown in the table.

Reviewer E

This is a single-center, retrospective study of No. 4L lymph node dissection for left upper lobe lung cancer.
This study has a small population and no new findings.
It is obvious that N2 patients have a poor prognosis, that dissection of No. 4L lymph node increases the frequency of recurrent laryngeal nerve palsy, and that the use of energy devices is a risk for recurrent laryngeal nerve palsy.
Table 1 is a confusing table, including both patients' characteristics and univariate and multivariate analysis. The method of analysis is also questionable: the cutoff values for each item in Table 1 and Table 4 are unclear, and in Table 4, the method of selecting univariate items is unclear. Is it possible that the analysis was done according to the author's convenience?

Reply: We are sorry to hear that you were not interested in this research. The objective of this study was to evaluate the relationship between the procedures to be noted during dissection and occurrence of RNLP to safely dissect the upper medial lymph node on left upper lung cancer without complications. Despite reports of poor prognosis for pN2, current guidelines only allow LN dissection of some areas of the superior mediastinum for left lung cancer. In response to this, the first half of the analysis was performed with the aim of clarifying the existence of occult metastasis. From the above, it was clear that accurate medial lymph node dissection was required. The vessel sealing system was mostly used in VATS, although the safety of its use has improved over the years. Of course, without caution, the use of energy devices will continue to pose a risk of anti-circulatory palsy, however, our findings show that it is a risk that can be reduced infinitely. In Table 1, the relationship between clinical factors and prognosis was evaluated by comparison between the two groups, and the cut-off values were also analyzed for the most appropriate values and the values before and after it. Only one of them is presented in the results. Evaluations were made for blood loss of 100, 200, and 300 mL and operation durations of 3, 4, and 5 h; however, no significant differences were found. Table 4 also shows the results of univariate analysis of all the clinical factors listed in the Methods. It was not intentional, as the reviewer opines.

Reviewer F

Thanks for giving me an opportunity to review the article entitled "Mediastinal Lymph Node Evaluation, Especially at Station 4L, in Left Upper Lobe Lung Cancer".

The main results of the study were as follows;
1. pN2 was an important predictor of recurrence.
2. #4L lymph node dissection was an independent risk factor for recurrent laryngeal nerve palsy.

However, they are well known knowledge. What is the novelty we can obtain from the study? We cannot find it.

This study was composed of two different studies.
One was about prognosis of 139 pts with left upper lobe lung cancer, and the other was about recurrent laryngeal nerve palsy in 91 pts who had video recordings of sufficient quality for evaluation. The authors should describe about that more clearly and definitively.
Reply: The objective of this study was to evaluate the relationship between the procedures to be noted during dissection and occurrence of RNLP for safely dissecting the upper medial lymph node on left upper lung cancer without complications. Despite reports of poor prognosis for pN2, current guidelines only

allow LN dissection of some areas of the superior mediastinum for left lung cancer. In response to this, the first half of the analysis was performed with the aim of clarifying the presence of occult metastasis. In the latter half of the evaluation, only 91 of 139 cases were targeted because a video to observe all dissection procedures was absolutely necessary. Of course, the evaluation was the best in the same target case, although unfortunately, this number was actually small.

The authors described their interpretation of the results obtained in RESULTS session. They should do it in DISCUSSION session.
Reply:
We have checked the Results and moved the text that explains the interpretation to the Discussion (Page 17, Line 261-Line 263).

Patient characteristics should first be described in Table.
Reply: We have created a new Table 1 to present the patients' characteristics and added an explanation at the beginning of the Results (Page 13, Line 182-Line 193).

In Table 3, it is difficult to understand what were compared for OS and DFS.
Why did the authors concluded "#4L LND should be performed" based on the results?
Reply: We are sorry for the incomprehensive explanation. As there was no difference in prognosis associated with lymph node metastasis in cases wherein station 4L LN was dissected, we further confirmed whether non-dissection of station 4L LN affected the prognosis. Since there were many cases whereby station 4L LN was not dissected as compared with other stations, we thought that there were some effects. Therefore, we investigated the effect of lymph node metastasis on the prognosis in all cases except those in which the condition of the lymph nodes was not confirmed at all. Unfortunately, there was no significant difference both for OS and DFS, although the 5-year DFS rate reduced in patients with # 4 LN metastasis (from 57.1% to 48.6%). The main reason for concluding that station 4L LN dissection should be performed is the fact that occult metastasis was found despite mediastinoscopy being actually performed, and the results in Table 3 have ancillary implications.

Surgical procedures being analyzed in Table 6 should be exemplified in the video.
Reply: Thank you for your suggestion. We have added Figure 1 instead of the video for correspondence. If you still prefer a video presentation, we can create it.

Reviewer G

Your study shows the important predictors of recurrence and risk factors for recurrent laryngeal nerve
palsy in NSCLC patients with left upper tumor. However, I think that there are two

major problems with your study.
First, I consider your conclusion of the importance N2 metastasis for recurrence is common for thoracic surgeons, and the importance is applicable not only left upper lobe but also other lobes. Your study is not novel. Second, I guess that you wanted to clarify the relationship between the prognostic factors and N2 metastasis, especially at station 4L. It is necessary to analyze them for all patients with dissecting lymph nodes at station 4L. Hence, I had difficulty interpreting your study for several reasons. Because your study has various objectives which included patients without dissecting #4L (page 12, Line 183-185) and excluded patients with node-positive at station 4L on mediastinoscopy (page 12, Line 179-180). You should need to determine inclusion criteria more strictly for your objects to clarify the relationship between the prognostic factors and lymph node metastasis at station 4L.
Reply: The objective of this study was to evaluate the relationship between the procedures to be noted during dissection and the occurrence of RNLP to safely perform dissection of the upper medial lymph node on left upper lung cancer without complications. Despite reports of poor prognosis for pN2, current guidelines only allow LN dissection of some areas of the superior mediastinum for left lung cancer. In response to this, the first half of the analysis was performed with the aim of clarifying the presence of occult metastasis. Therefore, as the reviewer points out, it is not surprising that pN2 is an important factor in the recurrence of all lobe-developing lung cancers, and there are several reports corroborating this fact. Certainly, the reason why station 4L LN metastasis did not affect the prognosis may be due to the effect of exclusion of patients with node-positive by mediastinoscopy or the existence of several undissected cases. However, preoperative induction therapy may affect the performance of the dissection procedure; thus, it was excluded. The evaluation including undissected cases may indicate the situation in the real-world settings. We have revised the last paragraph of the Introduction to make the purpose of the evaluation clearer (Page 8, Lines 96-99).

Although you concluded accurate mediastinal lymph node dissection, including 4L, should be performed, I disagree with your conclusion at least regarding dissection station 4L. Station 4L was not a prognostic factor for OS and PFS, on the other hand, it was an independent risk factor for recurrent laryngeal nerve palsy in your study. I think that your result may lead to the unnecessary dissecting of station 4L because of increased postoperative complications even though it does not contribute to survival.
Reply: Unfortunately, in our study, station 4L LN metastasis was not related to DFS and OS. However, some previous reports suggest an impact on the prognosis, and in fact, these are largely unclear. The purpose of this study was to evaluate surgical procedures to reduce the incidence of complications, especially recurrent laryngeal nerve palsy. It is a fact that there are cases of up-staging as a result of station 4L LND, and we believe that it is important to extract these cases. Of course, we believe that it is necessary to consider other detection methods, such as VAMLA (video-assisted mediastinoscopic lymphadenectomy) or EBUS / EUS, in the future. A part of the conclusion section has been revised such that the main conclusion comprises

standardization of the station 4L LND procedure (Page 20, Lines 300-307).

Please tell me the significance of mediastinoscopy in your study. I think that the results of mediastinoscopy are not necessary to clarify the relationship between prognosis and lymph node metastasis. However, I can understand the necessity of mediastinoscopy if your study excludes objects with preoperative N2 lymph node-positive patients by using it. To understand the importance of your study, it may be more useful to eliminate those sentences related to mediastinoscopy or reduce the content concerned with mediastinoscopy.
Reply: In this study, we propose that it is better to perform mediastinal LND from the thoracic cavity side as far as possible because there is an occult metastasis in station 4L LN despite the mediastinoscopy. In the past, we performed mediastinoscopy before lung resection even for cases without a definitive diagnosis of lung cancer; however, now, we routinely perform mediastinoscopy only for cases after a definitive diagnosis. However, for cN2 / 3 cases in preoperative evaluation, we actively performed mediastinoscopy before lung resection. The role of mediastinoscopy is very important because preoperative treatment is introduced for patients with node-positivity. We have had questions from other reviewers, because of which we would like to keep the content on mediastinoscopy; if the Editor recommends removing the information in Table 3 (Table 4 after revision), we are ready to oblige.

In an analysis for risk factors in table1, they should show the hazard ratio for each characteristic, and why not include tumor diameter or clinical T factors in table 1? They are generally one of the most important prognostic factors of prognosis for NSCLC patients.
Reply: We have created a new Table 1 to present the patients' characteristics and added an explanation at the beginning of the Results (Page 13, Line 182-193). In addition, the analysis results for clinical T factor and HR for each analysis are added to Table 1 (Table 2 after revision).

It might be helpful for the reader to show clinicopathological characteristics on a new table other than table1. Because we can't have sufficient information in table 1 to understand your study. To understand the patient's background and validity in your study, we need more detailed information including tumor size, pathological T(T1/2/3/4), pathological N(N0/1/2), lymphovascular invasion, and so on.
Reply: Please see our previous reply.

You should mention the number of performing FDG-PET in the sentence and table because you did not perform all cases. In addition, you should also mention the definition of node-positive lymph node not only CT but also FDG-PET.
Reply: The number of cases, whereby FDG-PET was performed is listed in the new Table 1. Regarding FDG-PET, according to Japanese guidelines, lymph nodes with FDG accumulation alone do not affect the staging. Therefore, we did not specifically mention the definition of node-positive lymph node not on FDG-PET. We deemed

patients to be positive for metastatic spread if the LN exhibited focally increased FDG uptake higher than the normal background and those that were asymmetrical. Therefore, this explanation has been added to the clinical information part in the Methods (Page 10, Lines 123-126).

To emphasize the importance of lymph node metastasis, it is necessary to mention the range of LND that includes the upper mediastinal LND in all patients or permitted only hilar LND.
Reply: Thank you for the helpful recommendation. From the results of this study, we believe that it is necessary to dissect the upper medial lymph node, including the hilar, for left upper lobe lung cancer to detect occult metastasis. Therefore, the following sentences are added to the Discussion: "Therefore, even if metastasis is negative in mediastinoscopy, dissection should be performed from the thoracic cavity side." (Page 17, Lines 257-258). In addition, since a high correlation was observed between pathological N1 (station 10 and/or 11) and LN metastasis at stations 4L and 5, the following sentence is also included in the discussion section: "Therefore, if pathological N1 is proven intraoperatively, active station 4L LN dissection should be considered regardless of the difficulty in performing the dissection procedure." (Page 18, Lines 274-276). In this study, we did not clarify the cases, whereby only hilar LND without upper mediastinal LND was recommended, because of which we cannot discuss selective LND.

Reviewer H

Thank you for the valuable feedback. Before replying to the following comments, we would like to mention some points on endoscopic mediastinal lymph node staging techniques using endobronchial ultrasonography and endoscopic ultrasound. The CHEST article from Liberman et al. proposes that this technique has a high diagnostic ability and may become a new gold standard in the mediastinal staging of NSCLC. However, at present, endoscopic ultrasound was used as this technique is not widespread in Japan, and only EBUS is used at our institution. Furthermore, because this investigation was retrospective in nature, EUS was not considered. The purpose of this study was to evaluate the safety of mediastinal lymph node dissection to detect cases of occult metastasis even in station 4L LN, which could not be diagnosed by mediastinoscopy. Naturally, lymph node dissection includes not only diagnosis but also metastatic lymph node resection as a treatment. We hope that this point is now clear.

Line 50 - what was the time to surgery from the initial staging? was adding EUS to Ebus considered as adding EUS to Ebus increases the negative predictive value especially station 4 L based on EUS studies by Hwanbo
Reply: In this study, the time to surgery from initial staging was approximately less

than a month.
Line 75 - what was the time to surgery from the initial staging?
Reply: Reference 10 states that patients underwent a chest CT scan within 30 days of surgery, and an integrated PET-CT within 40 days of surgery.
Line 106 - was preoperative endosonographic staging done?
Reply: We did not do this.
Line 121 - Have you considered adding EUS to Ebus in preoperative staging. If no explain why?
Reply: We did not consider adding EUS to EBUS for the reasons mentioned above.
Line 175 - What was the tumor size? Please add a table for all upstaged patients
Line 178 - what did the pre operative PET CT show? please add table of all upstaged patients
Reply: Since the focus of this study was the evaluation of station 4L lymph nodes, we created a table for up-staging cases on station 4L lymph nodes (below). However, although it does not seem necessary, if the reviewer deems it necessary, we are ready to add it to our manuscript.

case	Age (year)	Sex	FDG-PET[a]	cT	cN	cStage	Mediastinoscopy	approach	histology	pN	Metastatic LN[b]	recurrence	prognosis
1	54	F	5, 11	2a	0	IIA	done	Open	Ad	2	4L, 5, 6	N/A	Alive
2	69	M	4, 5	2b	2	IIIA	done	Open	Ad	2	4L, 5	Skin	Death
3	53	M	12u	1c	1	IIB	done	VATS	Ad	2	4L	N/A	Alive
4	47	F	11	1b	1	IIB	N/A	Open	Ad	2	4L	N/A	Alive
5	83	F	None	1c	0	IA3	N/A	VATS	Ad	2	4L, 5, 6	LN, Pl	Alive
6	76	F	None	1b	0	IA2	N/A	VATS	Ad	2	4L	N/A	Death
7	69	M	None	1c	2	IIIA	N/A	Open	As	2	4L, 5, 6	LN, Pul, Bo	Alive
8	78	M	None	1b	0	IA2	N/A	Open	NS	2	4L	N/A	Alive
9	81	M	None	2b	0	IIA	N/A	Open	Sq	2	4L	N/A	Alive

Ad, adenocarcinoma; Bo, bone; cT, clinical T factor; cN, clinical N factorF, female; FDG-PET, fluorodeoxyglucose-positron emission tomography; LN, lymph nodes; M, male; N/A, not applicable
NS, non-small cell carcinoma; Pl, pleura; pN, pathological N factor; Pul, pulmonary; Sq, squamous cell carcinoma; VATS, video-assisted thoracic surgery
a : lymph node station with FDG accumulation
b: metastatic station on mediastinal lymph node

Line 222 - Will adding EUS to Ebus would reduce the upstaged patients as combined approach has a higher negative predictive value and higher sensitivity compared to mediastinoscopy and can prevent futile thoracotomies. Please add reference of CHEST article from Liberman et al
Reply: We have added the content of the CHEST article from Liberman et al. to the Discussion section (Page 20, Lines 301-302).
Line 233 - Why was LND not done just to reduce operative time? Mention reasons
Reply: It mainly refers to high-risk patients who wanted shortened operation time.
Line 267 - Add a line on added value of EUS to Ebus in pre operative staging and that limitation of your study was that a combined Ebus + EUS wasnt done routinely and that may have picked up the occult positive Station 4 L as difficult station 4 L not accessible by ebus and mediastinoscopy can be accessed with EUS based on the combined EUS and Ebus articles
Reply: We have added the contents of the article from Liberman et al., Chest, to the Discussion section (Page 20, Lines 302-303).
Please make these above revisions and resubmit