

Peer Review File

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Reviewer A

Comment 1: Methods: The actual number of patients enrolled (563 and 304) belongs in the results section. Reply 1: Thank you for your suggestion. We have modified our text as advised. Changes in the text: Please see Page 7, line 6 and 9, and Page 12, line 5 -6.

Comment 2: How was selection for mVATS or uVATS done?

Reply 2: Thank you for your question. uVATS was started in February 2019 and the surgical procedure was decided by the surgeon. Although there is no clear definition, most cases were performed by uVATS since 2020. We have modified our text as advised. Changes in the text: Please see Page 8, line 10.

Comment 3: Results: In the last paragraph you state a number of confounding factors. What do they confound? N factor upstaging? Reply 3: Thank you for your comment. We performed multivariable analysis based on four confounding factors that are presumed to be related to N factor upstaging. Changes in the text: none

Comment 4: Discussion: Please add references in the first three paragraphs in some statements that you make. Reply 4: Thank you for your comment. There were references in the first paragraphs. The second and third paragraphs were where we had discussed our results, so there was no specific literature to cite. Changes in the text: none

Comment 5: Do you have an explanation as to why more lymph nodes were harvested in uVATS over mVATS?

Reply 5: Thank you for your comment. There are various reasons why the number of lymph nodes dissections in uVATS has increased. I think that the main reasons are the surgeon's proficiency and improved technique. I believed that as the number of uVATS operations increases, surgeons become more familiar with uVATS, and the number of lymph node dissections increases accordingly. Changes in the text: none

Comment 6: Could you say something about case selection? In which cases did you choose for uniportal and in which for multiportal?

Reply 6: Your suggestion is reasonable. We have modified our text as advised. Changes

in the text: Please see Page 17, line 2-3.

Reviewer B

Major comment

Comment 1: Have the authors performed uVATS and mVATS in parallel? Probably not. Perhaps they have practiced mVATS first, and then applied their experience to uVATS procedures? If that is true, then the results of this study are self-evident and have little novelty. - In my opinion, as I feel about this type of research, if appropriate lymph node dissection is performed, there should be no difference in quality due to differences in approach. If there is a difference, it is not because of the approach, but because of the poor quality of the surgeon's technique. In other words, I think that it is not meaningful to compare the quality of the procedure by approach at the same facility and by the same surgeon.

Reply 1: Thank you for your comment. It is true that we have not performed uVATS and mVATS in parallel. As you pointed out, first we have practiced mVATS, and then introduced uVATS. The main purpose of this study was to demonstrate that the quality of lymph node dissection could be maintained. But beyond that, we would like to share with more surgeons the procedures we have developed to maintain the same quality even as the approach becomes more difficult.

Changes in the text: none

Minor comment

Comment 1: Title: While the brevity is favorable, it does not accurately represent the purpose of this study.

Reply 1: Thank you for your suggestion. Our title may not be an accurate representation, but we chose brevity. We would keep the current form.

Changes in the text: none

Comment 2: p3, lines 56-57: "The appropriate surgical steps for the uniportal approach should be performed to ensure the quality of lymphadenectomy because this approach is technically difficult." - What are the authors trying to argue with this statement? Are the authors trying to state that uVATS needs its own surgical procedure? To begin with, what is the definition of "the appropriate surgical steps"?

Reply 2: Thank you for your comment. Thoracoscopic surgery began with a multiportal approach. Switching to a uniportal approach involves getting used to a different field of

view, new tools and so on. In order for surgeons to adapt to them, we believe that uVATS needs its own surgical procedure. We described the appropriate surgical steps in Methods.

Changes in the text: none

Comment 3: p4, line 70: "sublobar resection" - Since wedge resection is not included in major pulmonary resection, shouldn't the description here be segmentectomy?

Reply 3: Thank you for your pointing it out. I revised it. Changes in the text: Please see Page 7, line 8, and Figure 1.

Comment 4: p4, line 74: "gender" - I think it would be better to use "sex" here, since "sex" and "gender" have different connotations.

Reply 4: Thank you for your pointing it out. I revised it. Changes in the text: Please see Page 7, line 12, and Page 13, line 17, and Table 4.

Comment 5: p4, line 75 "smoking index (pack-year)" - This statement is incorrect. If it is to be listed, shouldn't it be "smoking history (or status) (pack-year)"?

Reply 5: Thank you for your advice. I revised it.

Changes in the text: Please see Page 7 line 12, and Table1,3.

Comment 6: In the surgical video, the structure and the text describing it are misaligned.

Reply 6: Thank you for your pointing it out. I fixed it. Changes in the text: none

Comment 7: p7, line 145: "The contribution of factors to N-upstage" - Wouldn't "The associated factors of N-upstage" be appropriate? Reply 7: Thank you for your pointing it out. This is a statistical term, so we would keep the current form. Changes in the text: none

Comment 8: p7, line 146: Please describe the confounding variables used in the multivariable analysis.

Reply 8: We stated the confounding factors in manuscript (Page 13, line9-12) and table 4. Changes in the text: none

Comment 9: p9, line 178 and Table 4: "Multivariate" - "Multivariable", isn't it?

Reply 9: Thank you for your pointing it out. I revised it.

Changes in the text: Please see Page 3, line 16, and Page 11, line 16, and Page 13, line 17, and Page 16, line 14 and Table 4.

Comment 10: p10, line 191: "This is the first report focusing on lymphadenectomy quality using the uVATS approach." - The article the authors cite as reference 15 discusses nodal upstaging of uVATS, which I believe focuses on the quality of lymph node dissection in uVATS. Reply 10: Thank you for your comment. Ismail et al¹⁵. described that the aim of their study is to evaluate the efficacy of lymph node dissection performed with the uVATS in their introduction. It may be a difference in interpretation, but we would keep the current form. Changes in the text: none

Comment 11: pp10-11, lines 213-214: The quality indicator of lymph node dissection is described in detail in the following article: Matsuura Y. Lung Cancer. 2021;152:78-85. Please refer to and cite.

Reply 11: Thank you for your comment. We refer to and cite. Changes in the text: reference 11

Reviewer C

Comment 1: Please detail your choice of surgical approach.

Reply 1: Thank you for your comment. uVATS was started in February 2019 and the surgical procedure was decided by the surgeon. Although there is no clear definition, most cases were performed by uVATS since 2020. We have modified our text as advised.

Changes in the text: Please see Page 8, line 10.

Comment 2: please perform a propensity matching score and reconsider. Otherwise, it difficult to conclude your opinion.

Reply 2: Thank you for your suggestion. In this study, propensity score matching was not considered effective as the population size was not large, so we did not use it. However, we followed your suggestion and verified it. First, uVATS (n=123) and mVATS (n=123) groups were matched 1:1 by sex, age, cStage, histology and ASA score. Operative time ($p<0.0001$) and postoperative drainage time ($p=0.0004$) were significantly better in uVATS group compared with mVATS group like the original manuscript. There was no significant difference in postoperative hospitalization time ($p=0.66$). Next, N upstage group (n=37) and non-N upstage (n=37) group were matched in the same way. We performed the same multivariable analysis as in the manuscript, only pathologic invasion size, but not approach, significantly contributed to N factor upstaging (invasion size, odds ratio: 1.02, 95% confidence interval:1.00-1.04, $p=0.02$; uVATS, odds ratio: 0.56, 95%

confidence interval:0.27-1.17, p=0.12). The results were the equivalent to our original manuscript.

Changes in the text: none

Reviewer D

Comment 1: the clinical stage should be comparable between the two groups and it seems that, but no statistical analysis was performed to assess that. Reply 1: Thank you for your comment. We have modified our text as advised. Changes in the text: Please see Table1, 3
Comment 2: How was the clinical stage assessed? what was the role of EBUS in this study? Reply 2: Thank you for your comment. The clinical stage was evaluated using CT and PET/CT as described in the manuscript. Of course, we also performed EBUS in cases where cN2 was suspected. Changes in the text: none

Comment 3: How were the lymph node counted? by the pathologist? by the surgeons?

Reply 3: The lymph nodes were counted by pathologist at our facility.

Changes in the text: none

Comment 4: in my opinion, all the lymph node dissection must include lymph node 7 for all lobe resection as assessed by the latest ESTS guidelines about lymph node dissection

Reply 4: Thank you for your comment. Selective mediastinal lymph node dissection/lobe-specific lymph node dissection has been performed at many institutions in Japan. In other words, lymph node 7 is not dissected during upper lobectomy. We do this at our facility as well. Changes in the text: none

Comment 5: the retrospective nature of this study should be clearly defined in the methods and also in the abstract

Reply 5: Thank you for your comment. I believe that the retrospective nature of this study was clearly defined in the methods and in the abstract.

Changes in the text: none

Comment 6: the power of this study is also low and only a randomized controlled trial could answer to the question raised by this study

Reply 6: Your comment is reasonable. As you pointed out, the total number of cases is relatively small, so a prospective, multicenter and randomized controlled study is required.

Changes in the text: none

Comment 7: the comparison is also affected by the surgical learning curve of the two procedures

Reply 7: Thank you for your comment. We agree with that, but it was not investigated in this study.

Changes in the text: none

Comment 8: the technical part of this paper should be reduced or deleted

Reply 8: Thank you for your suggestion. The main theme of this study is that the quality of lymphadenectomy could be maintained by using appropriate surgical steps. We spent a lot of time developing the procedures. It may seem long, but we would keep the current form. Changes in the text: none

Comment 9: morbidity (please check the table 1 for this typo) could be defined with a detailed list of the adverse events

Reply 9: Thank you for your comment. I revised it. Postoperative complication was defined as a complication occurring within 30 days from surgery. Complication were evaluated with the Clavien-Dindo version 2.0. We have added a description about this in the revised manuscript. Changes in the text: Please see Table1, 3, and Page 8, line 6-8.

Reviewer E

Comment 1: The type of lymphadenectomy should be clearly described (ND2a-1 has to be checked in the reference) while surgical steps of lymphadenectomies may be shortened.

Reply 1: Thank you for your comment. We added the statement of ND2a-1. The surgical steps were described in detail so that other surgeons can reproduce them. Changes in the text: Please see Page 9 line3 -8.

Comment 2: I would recommend checking if any difference in the number of harvested lymphadenectomy may be related to the learning curve thus comparing years of recruitment.

Reply 2: Thank you for your suggestion. We have not been able to consider that at this time. We believe that if we had been able to consider the content, the quality of this study would have been even higher. Changes in the text: none

Reviewer F

Comment 1: How many GGO type ADC were included in the study? Because, we could

find some opinions such as LN dissection for the GGO patients are useless. In other words, your study could have more power when excluding GGO type ADC.

Reply 1: Your question is reasonable. There were 8 cases of lung cancer with a solid size of 5mm or less in preoperative imaging. There were 26 cases of 10mm or less. However, lymph node metastasis was found in 1 out of 26 patients. Changes in the text: none

Comment 2: What is your indications for Uniportal and Multiportal VATS? U VATS showed better results for the similar stage patients in your study. Then, why did you do m-VATS? Reply 2: uVATS was started in February 2019 and the surgical procedure was decided by the surgeon. Although there is no clear definition, most cases were performed by uVATS since 2020. We have modified our text as advised. Changes in the text: Please see Page 8, line 10.

Comment 3: How could you guarantee that you did not perform a lymph node fragmentation? Usually, limited instruments could make more fragmentation.

Reply 3: Thank you for your comment. It cannot be said that the lymph node was not fragmented at all. However, we have basically used non-grasping technique which do not grasp the lymph nodes. Changes in the text: none

Comment 4: Extension of lymph node dissection was different between two groups. If then, two procedures could be compared? Such as, apple and orange cannot be compared

Reply 4: Thank you for your comment. There was certainly a significant difference in the extent of lymph node dissection between the two groups. Six surgeons performed these 21 surgeries (ND2a-2). 18 surgeries were performed under mVATS between 2017 and 2019. Clinical stage varied, but lymph node metastasis was observed in 6cases (28.5%). This is more than twice the value in Table2. Something might have occurred before or during surgery that make us suspect lymph node metastasis.

Changes in the text: none

Comment 5: More conversions could be found in the multiportal VATS groups. Were they included or excluded in the study? And the analysis of LN was considered the conversion?

Reply 5: Thank you for your comment. Of course, they were included in this study. There were 6 cases of dense adhesions of lymph nodes with the pulmonary artery among the converted cases. The reason for conversion was to control bleeding in 4 cases.

Changes in the text: none

Minor Comment 7: How do you measure pathological solid part? The term GGO and solid are kind of radiological term, not a pathologic.

Reply 7: Your comment is reasonable. We have modified our text as advised. Changes in the text: Please see Page 7, line14, and Page 13, line17 and Table1, 3 and 4.

Comment 8: What is Mobidity in Table 1

Reply 8: Thank you for your comment. I revised it.

Changes in the text: Please see Table1, 3.

Comment 9: What are ND2a-1 and ND2a-2?

Reply 9: Thank you for your comment. We added the statement of ND2a-1.

Changes in the text: Please see Page 9 line3 -8.

Reviewer G

Comment 1: Can the authors expand on rationale for Level 2 dissection?

Reply 1: This may not be the proper answer to your question. For example, LN#2R was dissected for right upper lobectomy. In selective mediastina lymph node dissection, the superior mediastinal lymph nodes were dissected during upper lobectomy. Is this the answer?

Changes in the text: none

Comment 2: is there any evidence to suggest that other surgeons practice lymph node dissection differently? Reply 2: Thank you for your comment. Wang¹⁷ et al. reported the different way of lymph node dissection with uVATS.

Changes in the text: none

Reviewer H

Comment 1: Please define ND, it may be a common terminology for Japan but not for the rest of the world.

Reply 1: Your question is reasonable. ND is node dissection. I revised it.

Changes in the text: Please see Page 9, line 3-8.

Comment 2: Any patients with neoadjuvat therapy or with the puspose of salvage surgery

Reply 2: Thank you for your comment. Unfortunately, because this study focused on the quality of lymph node dissection, we had not investigated the presence or absence of

preoperative treatment or salvage surgery.

Changes in the text: none

Comment 3: How are the patients selected into UVATS vs MVATS

Reply 3: Thank you for your question. uVATS was started in February 2019 and the surgical procedure was decided by the surgeon. Although there is no clear definition, most cases were performed by uVATS since 2020. We have modified our text as advised.

Changes in the text: Please see Page 8, line 10.

Comment 4: M VATS surgeries might have a learning period, and experienced could have performed by the more experienced surgeons.

Reply 4: Your comment is reasonable. Certainly, some surgeons had sufficient experience with mVATS. However, we believe that the appropriate surgical steps have played an important role in being able to maintain the equivalent quality as mVATS in a short period of time.

Changes in the text: none

Comment 5: It is very difficult to support the findings unless the patients were randomized.

Reply 5: Your comment is reasonable. As you pointed out, a prospective, multicenter and randomized controlled study is required.

Changes in the text: none

Comment 6: Authors claim shorter hospital stay, more LND, less bleeding and less duration of surgery with U VATS. I am wondering how they can explain this. At the beginning the study looks like non inferiority comparison to the standard technique which is MVATS. Please clarify the findings.

Reply 6: Thank you for your comment. Although this is a non-randomized comparison between uVATS and mVATS groups, it was described the reduction of postoperative hospital stay, blood loss and postoperative drainage period.

Changes in the text: none

Comment 7: Finally, what do authors recommend? Obviously their surgeons had a baseline experience with MVATS and then switched to UVATS. Now outcomes are better. Do they recommend a young surgeon to start UVATS without any experience?

Reply 7: Thank you for your comment. It is important to ensure patients safety, so we do not recommend one method over the other. However, since uVATS is currently the

standard surgery at our hospital, young surgeon performs uVATS without any experience with mVATS. Changes in the text: none.

Comment 8: Please describe the contributions of the findings. Reply 8: Thank you for your comment. It was shown that the quality of lymph node dissection was maintained. In the long term, the overall quality of surgery is considered to be the 5-year survival rate, but in the short term, it is considered to be the perioperative results. Our results show that they are comparable, and we intend to further improve our current technique. We also hope to be able to report long-term results in the future.

Changes in the text: none.

Reviewer I

Comment 1: During mVATS "uVATS" approach might be used (camera via main port). Do you think it would be beneficial during mVATS to consider uVATS to enhance lymphadenectomy? For example one of my colleagues prefers mVATS - he uses 2 ports, but a smaller, lower one is used for traction/stapler not for camera. The camera is used via the main port. Any thoughts on that?

Reply 1: Thank you for your comment. I had performed mVATS before, but the camera was only used via the camera port. However I don't have any experience with it, I think it's useful. Changes in the text: none

Comment 2: The article requires some language editing.

Reply 2: Thank you for your comment. The manuscript was revised by a native English speaker.

Changes in the text: none

Comment 3: ND2a-1 should be explained

Reply 3: Thank you for your suggestion. We added the statement of ND2a-1.

Changes in the text: Please see Page 9 line3 -8.

Comment 4: You excluded patients with no mediastinal lymph node dissection. I think those should be included - where there any differences between mVATS and uVATS? If so, why? Reply 4: The main theme of this study is that the quality of lymphadenectomy could be maintained by using appropriate surgical steps. Cases without mediastinal lymph node dissection were not considered. If we consider cases without mediastinal lymph

node dissection, it may be possible to study the quality of lobectomy between uVATS and mVATS. Changes in the text: none

Comment 5: what about LN# 8 and 9? I understand the rationale for excluding hilar lymph nodes but LN8 and LN9 should be included. Access to the pulmonary ligament can be sometimes challenging via a single port. Lymph nodes LN8 can be as challenging as LN7 (similar anatomical boundaries but lower).

Reply 5: Thank you for your comment. In selective mediastinal lymph node dissection during lower lobectomy, LN#8 and 9 were also dissected. There were no appropriate surgical steps for LN#8/9, but it was included in the results.

Changes in the text: none

Comment 6: Subsections of the Results part should be named for better clarity.

Reply 6: Thank you for your suggestion. We have modified our text as advised.

Changes in the text: Please see Page 12, line 4 and 15.

Reviewer J

Comment 1: The data of patient backgrounds lack the height, body weight, and body-mass index of the patients. This information is important, so it should be added to the manuscript. Reply 1: Thank you for your comment. We have modified our text as advised. Changes in the text: Please see Table 1,3.

Comment 2: Indeed, there are some reports indicating that the operation time is shorter in uVATS than that in mVATS, but I wonder why it occurs since, as the authors mentioned, there are more instruments inserted in mVATS than in uVATS. Why was the operation time in uVATS shorter than that in mVATS in this study? Did it derived from less cases undergoing ND2a-2 lymph node dissections in uVATS group? Or, was it because senior surgeons usually performed uVATS, while junior surgeons usually performed mVATS? How do you decide whether uVATS or mVATS is selected for patients in your institution?

Reply 2: Thank you for your comment. We think that the smaller number of ND2a-2 lymph node dissection is probably not a major reason. Lymph node dissection of one zone takes about 20-30 minutes. On average for the mVATS group, it only adds about 4 minutes. We think that the main reason is which uVATS is faster to operate than mVATS for senior surgeon. Coordination with the assistant is important for mVATS, but it may take time to adjust to the assistant's movements. On the other hand, uVATS is solo surgery, which

allows for faster work for senior surgeon. Surgical procedure for mVATS or uVATS was decided by surgeon at our institution. uVATS was started in February 2019 and the surgical procedure was decided by the surgeon. Although there is no clear definition, most cases were performed by uVATS since 2020.

Changes in the text: none

Comment 3: How is the methods in your institution to train uVATS operators? Do junior surgeons start anatomical lung resections by uVATS initially?

Reply 3: Thank you for your comment. Since uVATS is currently the standard surgery at our institution, young surgeon performs uVATS without any experience with mVATS.

Changes in the text: none

Comment 4: Hilar lymph node dissection is as important as mediastinal lymph node dissection. Are there any appropriate surgical steps in your institution?

Reply 4: Your question is reasonable. Although hilar lymph node dissection is certainly important, there is no appropriate surgical steps.

Changes in the text: none

Comment 5: There were 8 conversions to thoracotomy in uVATS group and 12 conversions in mVATS group. Please indicate the reasons for conversion.

Reply 5: Thank you for your comment. The reasons for conversion in uVATS were dense adhesions of lymph nodes with the pulmonary artery (3cases), pleural adhesion (1), unknown location of tumor (1), bleeding (1), bronchial injury (1), device trouble (1). On the other hand, the reasons for conversion in mVATS were bleeding (3cases), dense adhesions of lymph nodes with the pulmonary artery (3), pleural adhesion (3), unknown location of tumor (1), bronchial injury (1), severe incomplete fissure (1).

Changes in the text: none