

Peer review file

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Reviewer A

Overall comment. Zhao and colleagues report "Uniportal versus Multiportal Thoracoscopic Sleeve Lobectomy for the Surgical Treatment of Centrally Located Lung Cancer: A Single Institution Experience".

Although the study has several limitations such as single-institutional retrospective nature and small sample size, the design of this retrospective study is logically well-established. Consequently, the excellent results of the authors are reasonable, and they are discussed well.

More than anything, the paper includes several novel and important information. Those are the comparison of surgical outcome between uniportal and multiportal thoracoscopic sleeve lobectomy and the survival outcome of uniportal thoracoscopic sleeve lobectomy.

Therefore, the paper has a sufficient value for publication in the JTD journal.

Congratulations on your great work.

Reply: Thanks for your positive comment and we are grateful that our manuscript meets your standards for publication. However, limits exist and we have made essential revisions as the other reviewers suggested. We hope the revised version will improve and perfect our manuscript.

Reviewer B

Overall comment. First of all, my curiosity about this paper is who conducted the multiportal approach and how the patients were assigned to each procedure? I understand it was decided by the discussion of the MDT but is there any criteria? Also, I understand the same surgeon did the uniportal approach for the 8 cases out of 12 cases and the learning curve you provided looks reasonable and excellent. Then, how about the multiportal approach? My concern is that this paper just describes the performance between each surgeon, not procedure.

Additionally, throughout the manuscript, please describe the actual number when you want to show the p-value.

Reply: Thank you very much for this critical comment. All patients in our department will be discussed through an MDT meeting prior to surgery. This MDT meeting consists of all our thoracic surgeons and also the radiologist, medical oncologist, and pathologist. The final procedure was fully discussed especially for patients who warranted VATS sleeve lobectomy. The criteria for a VATS sleeve lobectomy are described in section "Patient enrollment", however, whether to perform uniportal or multiportal is mainly depend on the operating surgeon's experience. The MDT team would make a full evaluation and give the final approval. Hence this retrospective study merely collected

cases received VATS sleeve lobectomy and were unable to elaborate on the criteria of how the patients were assigned to each procedure.

As mentioned, of the 12 uniportal cases, 8 operations were conducted by the same surgeon (Dr. J Zhao), hence we decided to conduct the learning curve analysis for this limited case. The CUSUM learning curve conducted by the same surgeon demonstrated a continuous phase of experience acquisition, however, the universality will be inevitably compromised. On the other hand, our initial purpose was to conduct a thorough analysis of uniportal sleeve approach, and the detailed description, as well as the learning curve for multiportal approach, has been reported by other studies, hence we consider it unnecessary to report the further analysis for multiportal approach. Nevertheless, we totally understand your concern that this paper just describes the performance between each surgeon, not procedure. As a complicated procedure, uniportal sleeve lobectomy is rarely performed, which makes the reverent study scarce and defective. However, we consider it necessary to conduct analysis on the basis of the current data, certain implications are to be noted regardless of the limitations that existed in study design and sample size.

Thank you so much for your advice on the actual number are needed with the p-value. We have made revisions throughout the revised manuscript with tracks.

Comment 1. In abstract, please describe actual value or number of each group not only the p-value like you did in the result part.

Reply: Thank you so much for your careful check. As your suggestion, we have already made correction in our revised manuscript. We hope that this revised version of abstract will meet your requirements.

Comment 2. In terms of study design, how did you assign the patients to each group/procedure? This question is the same as the overall comment above. The reason why I got this question is because you showed 6 surgeons who have 200 cases annual operation did the procedure but only one surgeon did 8 cases with uniportal approach. You also mentioned about the MDT to determine the approach but it does not make sense because of this distribution even though the small sample size of the patients.

Reply: Thanks for this critical comment. As we replied above in the overall comment section, the final procedure was fully discussed by the MDT team for patients warranted VATS sleeve lobectomy, however, whether to perform uniportal or multiportal is mainly depend on the operating surgeon's experience. The MDT team would make a full evaluation and give the final approval. Most of the uniportal approaches were performed by the same surgeon, and the other uniportal and multiportal approaches were performed by all six surgeons. Due to the retrospective nature of this study, no elaborate criteria for patient assignment was obtained as the prospective study demanded. We wonder whether this reply answered your query and willing to make a

further explanation for your need.

Comment 3. In discussion, you described that “the uniportal approach provided obvious advantages in aspects of chest drainage duration and volume compared to the multiportal approach. This may be largely due to the decrease in surgical incisions” but I don’t agree with this sentence because it sounds not reasonable because having additional two or three port cannot make such a big difference. This results also brought me the same question as comment 2.

Reply: Thanks for your comment. Due to that our results showed a significant decreased chest drainage duration and volume of uniportal approach compared with multiportal approach; we assumed this may be largely due to the decrease in surgical incisions. However, based on your comment, we realize it is superficial and incomplete for the explanation. The chest drainage duration and volume are influenced by various factors, such as surgical type, operation time, patients’ conditions, and et al. Hence, we made correction for this expression in the revised manuscript with tracks (See Page 8, Line 14-16). We hope this will no longer cause misunderstanding.

Comment 4. In discussion, it is described that complete continuous suture throughout the anastomosis was applied and it could achieve satisfying results. I can understand your opinion and some important technical benefit are described here but is there any other previous study to be cited? Also, it sounds little bit much to say that “Without a single knot placed in the bronchial lumen, this kind of anastomosis may minimize the possibility of postoperative symptoms and anastomotic stricture” because this is just an assumption and not investigated at all in this study.

Reply: We appreciate this query and comment. For the satisfying results obtained from continuous suture, study conducted by Chen et al. [Ref 14] achieved similar results. We added the citation as you required in the revised Discussion section (See Page 10, Line 9). The reference is also attached below for your convenience. Besides, as you mentioned above, the assumption seems inappropriate and we made corrections for this statement of “Without a single knot placed in the bronchial lumen, this kind of anastomosis may minimize the possibility of postoperative symptoms and anastomotic stricture” (See Page 10, Line 10-11).

Comment 5. In Figure 2, I got confused because you described that uniportal group had 12 patients while multiportal group had 20 patients in the manuscript, Figure 1 and Figure 2. Please check this figure and fix it if you need. In addition, please add specific survival duration or percentage in follow up information in the result not only the p-value.

Reply: Thank you so much for your careful check. We felt very sorry for any confusion caused by this mistake in Figure 2. We have already made correction in our revised manuscript. Meanwhile, the revised figure is also showed as below for your convenience. As your suggestion, we also added detailed survival information in the

Follow-up information (See Page 7, Line 9-13).

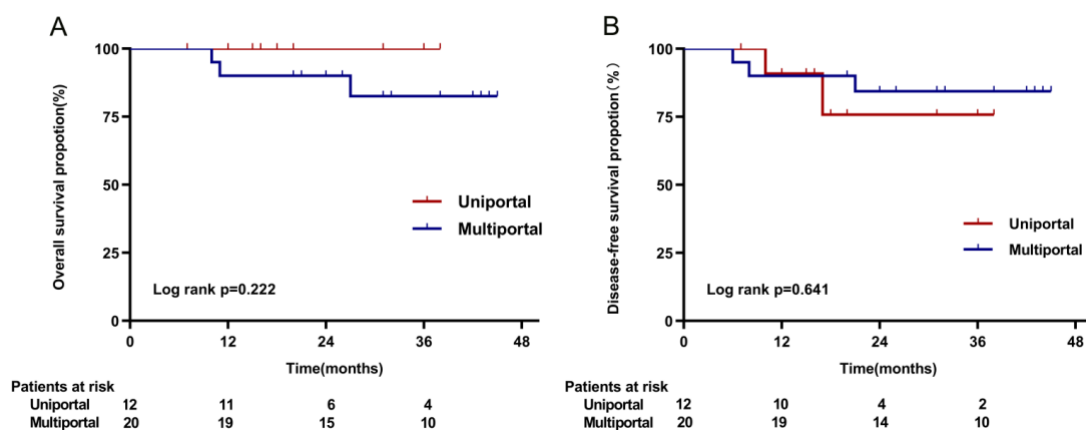


Figure 2: Kaplan-Meier curve for OS (A) and DFS (B) by the uniportal and multiportal approach.

Comment 6. In Table2, is staging based on preoperative information or pathological findings? Please describe both of them in detail including each T, N, and M factors if possible.

Reply: Thanks for your query. In Table 2, information of the TNM stage was based on the pathological evaluation. All the cases were M0 disease. We added the detailed information of T and N stage as you recommended in the revised table (See Table 2 in the revised version).

Comment 7. Lastly, I understand you simply want to compare the procedures but the surgical outcome from the patients who were excluded in this study (Figure 1, N=8) can also bring a thoughtful discussion. Do you have any comments on this?

Reply: Thanks for your comment. We totally understand your concern that the excluded cases are worth well analyzed. The purpose of this study is to make a comparison between uniportal and multiportal approach. As we all know that a better comparison research is to delaminate potential bias as possible. The introduction of preoperative chemo or radiotherapy will largely influence the selection or the process of procedure. As you can notice, patients received preoperative chemo or radiotherapy were prone to be assigned to the multiportal approach, inclusion of these patients will inevitably cause bias and imbalance between two groups. Hence, under serious consideration, we decided to exclude those patients from analysis despite the shrunk sample cases. However, we totally agree with your comment and we consider it a further study is needed with all of the eligible cases included after acquisition of an adequate number of cases. This will bring significant results and thoughtful discussion

Reviewer C

Comment.

What are we talking about..... "an incision or more". The feasibility of VATS sleeve is well known (Chen 2016, Ma 2018, Koryllos 2018). Whether we do it by single, bi- or tri-port depends on the surgeon's preference. How much more information do we get from 30 patients????

Furthermore, 8 patients are divided into learning and experienced phase! Why should we have more blood loss or chest tube drainage days because we make 1, 2 or 3 incisions. There must be a bias.

The technique of the anastomosis is discussed; this has nothing to do with the type of approach.

Reply: Thank you for this critical comment.

As you noted that the feasibility of VATS sleeve lobectomy has been reported. Chen et al. [Ref. 14] reported eight cases of single-port VATS sleeve lobectomy in 2016, Ma et al. [Ref. 15] reported eleven cases of complete VATS sleeve lobectomy, and Koryllos et al. [Ref. 18] shared their surgical technique based on the summary of 38 cases of uniportal VATS sleeve lobectomy. However, all the studies are limited in the form of case series or surgical technique. As a technically demanding operation, uniportal VATS sleeve lobectomy has not been applied universally due to the increased complexity and unevaluated surgical outcomes. The decision of the surgical approach for sleeve lobectomy does depend on the surgeon's preference as you stated, however, as an evolution of conventional VATS technique, uniportal approach should be applied more broadly for the treatment of pulmonary disease. By the way, the benefits of uniportal approach versus multiportal approach for lobectomy or segmentectomy has been discussed in previous literature [Harris et al. 2016; Wang et al. 2017; Lin et al. 2018], hence, in our humble opinion, we consider it necessary to conduct a comparative study between uniportal and multiportal VATS sleeve lobectomy.

Although the sample size was small in our study, we believe that our results have certain significance. Apart from the procedure technique we shared from our institution, the safety and efficacy of uniportal approach versus multiportal approach were mainly analyzed. The feasibility of uniportal sleeve lobectomy was first discussed. On the other hand, through this study, we are confident in achieving comparable or even better outcomes with a uniportal approach compared with multiportal approach. Hence, we consider it worthy of sharing and this may serve as further proof for the application of the uniportal approach for sleeve lobectomy.

As noted in our manuscript, the uniportal approach resulted in a significantly shorter chest drainage duration and a smaller chest drainage volume than the multiportal approach. Hence, we made the assumption of this may be due to the decrease in surgical incisions. However, based on your comment, we realize it is superficial and incomplete for the explanation. The chest drainage duration and volume are influenced by various factors, such as surgical type, operation time, patients' conditions, and et al. We made correction for this expression in the revised manuscript with tracks (See Page 8, Line 14-16). However, our result showed no difference in the estimated blood loss between the two groups. Admittedly, certain bias exists in our manuscript, however, we have made efforts to reduce selection bias for excluded patients received preoperative chemo or radiotherapy.

As you stated, the technique of the anastomosis is discussed and this has nothing to do with the type of approach. We totally agree with your opinion and the anastomosis technique used in the uniportal approach and the multiportal approach does resemble. Hence, we did not repeat the description of how this technique will be.

We wonder whether this reply answered your query and willing to make a further explanation for your need. We sincerely hope that you may take some time to reconsider our revised manuscript and give us the opportunity for manuscript revision or publication.

Reviewer D

Comment 1. I think the surgeries were performed in a single institution. In fact, uniportal VATS lobectomy is not a very popular surgery. Please mention how much experience the authors' institution have with the uniportal VATS in the 'method' section.

Reply: Thank you very much for this comment. As noted in the Operative procedure section in Patients and methods, all operations were performed by a total of six surgeons whose annual operating volume surpassed 200 cases in our department. We forget to provide detailed information of uniportal VATS experience. The uniportal VATS was already applied as conventional approach for regular pulmonary surgeries since 2015 at our institution. Hence, our surgeons have already gained sufficient for uniportal approach, however, special consideration for approach selection is needed for more complicated surgeries. For sleeve lobectomies, surgeons may prefer the multiportal of open-thoracic approach. In another word, the 200 annual procedures per surgeon were nearly all performed via uniportal VATS. We have already made essential modifications in the Method section of the revised manuscript (See Page 4, Line 16-17). We hope that this revised version of the abstract will meet your requirements.

Comment 2. Please explain in more detail in which cases the author did uniportal VATS and in which cases the author did multiportal VATS. Please elaborate on what efforts

you have made to reduce the selection bias in this study.

Reply: Thanks for your suggestions. We feel sorry for this insufficient information of patient who underwent uniportal or multiportal VATS. As noted in the manuscript, we retrospectively reviewed all patients who underwent thoracoscopic sleeve lobectomy for centrally located lung tumors from January 2016 to December 2018. The patients were then categorized into uniportal and multiportal groups. The detailed information in both groups was also portrayed in the Result section and Table 1, 2. We intend to include another table to illustrate the detailed information of each patients enrolled into analysis, however, this seems to be replicated and redundant. As for the approach selection for sleeve lobectomy, the final decision for uniportal or multiportal VATS was fully discussed by an MDT team, which would make a full evaluation of the patient's condition and surgeons' experience and give the final approval.

As noted in the Patient enrollment section, the introduction of preoperative chemo or radiotherapy will largely influence the selection or the process of procedure and inclusion of these patients will inevitably cause bias and imbalance between two groups. Hence, under serious consideration, we decided to exclude those patients from analysis. The effort to reduce the selection bias seems vague in the original manuscript, hence we made modifications in the revised manuscript (See Page 4, Line 10-11). In addition, as illustrated in the first paragraph of the Results section, the two groups showed no significant differences in demographic variables, which served as another proof for our effort to reduce the potential selection bias.

Comment 3. In 'method' section, describe in detail the differences of surgical techniques between uniportal VATS bronchial anastomosis and multiportal VATS bronchial anastomosis.

Reply: Thanks for your suggestion. However, the anastomosis technique used in the uniportal approach and the multiportal approach is similar, which is the end-to-end continuous suturing method. As noted in the Operative procedure section, this technique was reported in detail by Ma et al. [Ref 15]. Hence, we did not repeat the description of how this technique will be. Certain differences may exist in some aspects between uniportal and uniportal approach, such as the anastomosis time and the position of the instrument, however, the major technique used was similar regardless of the approach selected. We wonder whether this reply answered your query and willing to make further explanation or revision for your need.

Reviewer E

Comment. This study is nicely to compare sleeve lobectomy through multi vs uniportal VATS. This high-end technique was well presented and compared statistically so; it is worthy to be published.

Reply: Thanks for your positive comment and we are grateful that our manuscript meets your standards for publication. However, limits exist and we have made essential revisions as the other reviewers suggested. We hope the revised version will improve and perfect our manuscript.