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Reviewer A

This paper presented by Singh, et al. evaluated the surgical outcome of vein-first or artery-first lobectomy.

There are 2-groups of vein-first and artery-first. However, decision criteria of procedures are not clear. Since it is not clarified, this study would have a strong selection bias. Regarding with smoking status and tumor location, these 2 groups had a different background.

Artery-first group contains the patients who had a surgery with artery-vein-artery order. It is not a strict artery first group.

Reply: We thank you for your review. The decision on whether to go ahead with the division of the artery first vs the vein first was left to the discretion of the surgeon. We acknowledge that there may be some selection bias at play, however Table 1 shows that the groups are quite similar, with the only significant difference being a higher percentage of patients with a tumor ≤ 2 cm in the vein-first group. This would be more likely to result in improved survival for the vein-first group. In spite of this, no difference was seen. A multivariate analysis has also been performed to try to mitigate the effect of this difference. We acknowledge also the fact that the artery-first group contains artery-vein-artery patients. However the principal motivation behind doing this study was to determine whether or not the improvement in survival with a vein-first strategy (thought to be the result of decreasing circulating tumor cells) would be seen in this group of robotic lobectomy patients. In addition, in the “real world” sometimes dictates that the vein needs to be divided before all the arteries can be reached. We believe that our results are useful given their real-world applicability.

Reviewer B

Interesting work on the effects of ligation of the vein first in lung resections in relation to the presence of relapses of the disease.

As the authors acknowledge, since robotic surgery is a minimally invasive procedure, the surgical manipulation of the piece is minor and this will have a determining influence on less dissemination. The other aspect is the size of the tumor, surely in the future with the generalization of lung cancer screening, the operated tumors will be smaller. Although more studies are needed in this regard, if the findings are confirmed in the future, the surgeon will be able to decide between artery or vein ligation based on its accessibility and the safety of the procedure.

Reply: We thank you for your review.

Reviewer C

The authors retrospectively evaluate the outcomes between patients who undergo robotic lobectomies for non-small cell lung cancer using a vein-first vs. artery-first technique. They found that choosing a vein-first vs. artery-first technique for a robotic lobectomy does not significantly impact overall survival or cancer recurrence for patients with non-small cell lung cancer.

The surgical procedure and its potential impact on cancer prognosis is important to all surgeons. The content of this paper is very interesting.

I have the following concerns.

Comment 1

Since there is insufficient information about prognosis, the authors need to fill them in. Details of the rates of local recurrence, pleural dissemination, and distant metastasis due to hematogenous metastasis need to be provided.

A more detailed examination of the recurrence type would allow meaningful analysis of the order of surgical vascular processing and the possibility of hematogenous distant metastasis.

Reply: Recurrence-free survival rates are provided in the Kaplan-Meier curve in Figure 2. We agree that the pattern of recurrence would be useful information. Further details regarding location of recurrence, unfortunately, were not available.

Comment 2

Please provide additional details on the cause of death.

Since the primary endpoint of this paper is prognosis, data on recurrence and cause of death should be added. In addition, tables should be utilized to show the results for better clarity.

Reply: Recurrence-free survival rates and overall survival rates are provided in this study. Unfortunately, causes of death were not available. The survival rates are depicted in Figures 2 and 3 and therefore tables are not necessary.

Comment 3

Table 2.

Please list p-values for pathology stage III.

Reply: The p-value for pathology stage III has been added to Table 2.

Changes: Added p-value 0.063 for pathology stage III on Table 2 (page 14)

Comment 4

Table 2.

Patients with small cell lung cancer included. This is inconsistent with the title and methodology of the paper. Once again, the methodology, data analysis, and interpretation of the results need to be reviewed.

Reply: We have now excluded small cell lung cancer patients. We have adjusted the data analysis accordingly as well.

Changes: The numbers within the text of the results section have been updated to reflect the change in numbers after excluding the small cell lung cancer patients (page 5-6). We have also updated the data accordingly in Tables 1-3 and Figures 1-3.

Comment 5

The analysis includes patients with stage IV disease and includes patients for whom radical resection was not obtained pathologically. Did the authors evaluate stage IV patients for recurrence in the same way as other patients?

Reply: Recurrence in stage IV patients was evaluated in the same fashion.

Comment 6

In the statistical analysis in the text, the authors state that continuous variables were analyzed using mean values, but Table 3 lists median values. Please double check the analysis method and results for continuous variables.

Reply: We analyzed both mean and median values for continuous variables, but reported median for variables that were related to time, such as postoperative length of stay.

Changes: Added “or median” and “Median values were used for time-related continuous variables” on page 5.

Comment 7

Please clarify the criteria by which recurrence was diagnosed. In addition, please clarify the protocol for postoperative surveillance.

Reply: Details on criteria for recurrence were added. Postoperative surveillance was performed at 6 month intervals with CT chest and clinic visit for the first 2 years, then annually thereafter.

Changes: Added “Recurrence was defined as a new abnormality or lesion(s) seen on CT scan, confirmed by by PET-CT scan, repeat CT scan (to document growth), and/or biopsy.” (page 4).

Comment 8

Although controversial, previous papers have shown that middle lobectomy has a better prognosis compared to other lobectomies. Furthermore, current smokers have been shown to be associated with poor postoperative outcomes.

The bias of resected lobes and patient smoking status cannot be ignored in the analysis.

These prognostic factors are only examples, but more mature analyses are warranted.

Reply: A multivariate analysis has been provided.

Comment 9

Discussion is inadequate. You should review the endpoints of this paper again and develop a discussion that addresses them. The second endpoint should also be mentioned in the discussion.

Reply: We have expanded our discussion.

Changes: We have added the following text. “We found no significant difference in overall and recurrence-free survival between our two groups. Furthermore, both groups also did not significantly differ in the incidence of postoperative complications or in length of hospital stay.” (page 6)

“Furthermore, a study by Duan et al suggests that the timing of vein-first ligation, early versus late, may play a role in outcomes as well. This study found that ligating the vein immediately during VATS lobectomy (early ligation group) resulted in decreased dissemination of circulating tumor cells when compared to ligating the vein later once the artery, bronchus, and pulmonary fissure were partially or completely exposed (late ligation group). This finding also introduces the possibility that even with a vein-first technique, the timing of vein ligation may also play a role in tumor cell dissemination and therefore recurrence and survival.

The decision about whether or not to ligate the vein first during lobectomy for non-small lung cancer is often dictated by the particular anatomy of the specific patient. That said, certain trends with regards to vessel to be divided first do exist. For instance, we found that vein-first ligation was more likely in patients undergoing right upper and middle lobectomy. In both of these instances, it is often simpler to ligate the vein prior to the artery given the relative location of the vessels. We believe that this is due to the position of the vein relative to the arteries (for instance, the middle lobe vein is peripheral/medial to the artery in patients). In certain instances, such as when a posterior ascending artery is easily accessible after dividing the right upper lobe bronchus, or when a right middle lobe artery is traveling in a complete oblique fissure, it can be easier to ligate the artery first when doing the respective lobectomy. However the more common anatomic configuration is such that the vein is ligated first in these operations. On the other hand, left upper lobectomy was more commonly performed in an artery-first manner in our study. This is because the apicoposterior artery is often easily isolated and ligated with the lung retracted in an anterior fashion during the initial hilar/mediastinal nodal dissection. In the absence of evidence suggesting that the order of vessel division impacts oncologic outcomes, it is reasonable to state that these decisions can and should be based on convenience, safety, surgeon experience and comfort level, and ease, rather than biased towards a vein-first approach to provide a hypothetical benefit of reducing circulating tumor cells.” (pages 7-8)

Reviewer D

In this study, Vein-First vs. Artery-First Robotic Lobectomy Outcomes in Non- Small Cell Lung Cancer: A retrospective study were introduced. The authors report that robotic lobectomy does not significantly affect overall survival or cancer recurrence for patients with non-small cell lung cancer.

However, this paper lacks a logical and systemic explanation. Overall, the content of the discussion is poor. So, I think this paper needs a major revision.

I would like to point out some things that need to be improved.

Minor revision

1. In the Methods section.

It is recommended to add people who have performed lobectomy and their experience.

Reply: We have made the recommended changes. It is difficult to characterize the objective experience of surgeons especially given the broad time period of the study and do not believe this is relevant to the outcome of the study, nor do most studies comment on experience level – that said, if there is a sensible way to accomplish this in the context of the manuscript we are open to suggestions.

Changes: Added “from two surgeons” (page 4).

Major revision

1. Discussion section, L 139-140.

In particular, a vein-first technique was performed more often for small tumors (<2cm),

I could not confirm the data that the vein-first technique was performed more frequently for small tumors (<2cm). Please clarify this part.

Reply: We have provided the data for this.

Changes: We have added the following text. “Of note, a V-first technique appeared to be used more often for patients with tumors ≤ 2 cm in size than an A-first technique (50.68% v. 29.89%, $p=.002$)” on page 5. Also added tumor size data to Table 1.

2. Discussion section, L 139-141.

a vein-first technique was performed more often for small tumors (<2cm), along with On the other hand, an artery-first

RUL and RML lobectomy have been performed in the vein-first technique and LUL lobectomy in the artery-first technique, and we recommend explaining why.

Reply: We have provided additional discussion about this.

Changes: We have added the following text. “The decision about whether or not to ligate the vein first during lobectomy for non-small lung cancer is often dictated by the particular anatomy of the specific patient. That said, certain trends with regards to vessel to be divided first do exist. For instance, we found that vein-first ligation was more likely in patients undergoing right upper and middle lobectomy. In both of these instances, it is often simpler to ligate the vein prior to the artery given the relative location of the vessels. We believe that this is due to the position of the vein relative to the arteries (for instance, the middle lobe vein is peripheral/medial to the artery in patients). In certain instances, such as when a posterior ascending artery is easily accessible after dividing the right upper lobe bronchus, or when a right middle lobe artery is traveling in a complete oblique fissure, it can be easier to ligate the artery first when doing the respective lobectomy. However the more common anatomic configuration is such that the vein is ligated first in these operations. On the other hand, left

upper lobectomy was more commonly performed in an artery-first manner in our study. This is because the apicoposterior artery is often easily isolated and ligated with the lung retracted in an anterior fashion during the initial hilar/mediastinal nodal dissection. In the absence of evidence suggesting that the order of vessel division impacts oncologic outcomes, it is reasonable to state that these decisions can and should be based on convenience, safety, surgeon experience and comfort level, and ease, rather than biased towards a vein-first approach to provide a hypothetical benefit of reducing circulating tumor cells.”

3. Discussion section, L 145.

These findings are consistent with the study....by Refaely et al. (5).

The authors compared it with a study of non-robotic lobectomy presented by Refaely. However, the above study is open lobectomy. VATS lobectomy is being performed more frequently and is similar to robotic lobectomy.

Therefore, it is recommended to compare with the study results of vats lobectomy.

Also, a discussion of the above should be included in the discussion section

Reply: We have provided additional discussion about this along with a reference that studied this topic on VATS lobectomy patients.

Changes: We have added the following text: “These findings are consistent with the study of open lobectomies by Refaely et al, along with the study of VATS lobectomy by He et al. Given that VATS lobectomy is considered more similar to robotic lobectomy, the findings of He et al may be more comparable to our study. In the retrospective study by He et al, it was found that the order of vessel ligation during VATS lobectomy did not affect long-term survival of patients, which is consistent with our findings.” (page 7)

Reviewer E

Derail procedure of robotic lobectomy including ports placement should be described. When authors perform mediastinal lymph node dissection, before or after lobectomy? The timing could influence to the time of tumor manipulation. Some group routinely performs the LN dissection before lobectomy.

I am curious about the postoperative DFS or OS in stage II-III patients, which could have frequent circulating tumor cells or tumor cell spread during operation.

IRB number should be included in Method.

Reply: We have provided some basic details about technique and added a reference. We have included information about the order of mediastinal lymph node dissection. We have provided the IRB number in the Methods section. Multivariate analysis has been added, and includes pathologic stage.

Changes: “Mediastinal lymph node dissection was performed prior to division of vessels and the performance of lobectomy in all cases.” “Protocol number 300001851” (page 4). “Robotic lobectomy was performed with a completely portal technique using four robotic arms and an assistant port. The camera port was typically located in the 7th or 8th intercostal space. Our technique has been described previously¹⁷.” (page 4).

Reviewer F

The authors demonstrated the impact of the vein-first and artery-first methods in robotic lobectomies. This topic is continuously discussed very often in the field of thoracic surgery. I would like to make some comments on this manuscript.

1. I agree with the authors' opinion that "the order of division of vessels are often dictated by the necessities of anatomy and what is deemed safer or easier rather than an a priori decision to divide all arteries before the vein". Hence, I cannot understand what the purpose of this study is.

Besides, the results of their study show only that they could not reject the null hypothesis of no significant difference between the two groups, which does not prove that there is no significant difference between the two groups. If they really want to prove that there is no difference, they should conduct a non-inferiority trial with a larger number of cases.

Reply: We understand and agree that anatomy can change the preferred approach to lobectomy. Perhaps our wording is too strong. There are, at times, different ways to approach a particular lobe to be resected – therefore the question as to whether or not there is an advantage from an oncologic point of view to divide arteries first as opposed to veins is a relevant one. Other studies have demonstrated the increased incidence of circulating tumor cells in patients who undergo artery-first division (<https://jamanetwork.com/journals/jamasurgery/fullarticle/2732431>.) This study was an attempt to determine whether or not this biologic phenomenon would translate into any differences in outcome. We agree that larger studies may have a better chance at detecting differences between these two groups but do believe that a study of our size still has value.

Changes: We have changed “dictated” to “influenced” in the study (page 8).

2. A-V-A cases must be not the same as A-V cases regarding tumor cell manipulation, therefore these cases should be omitted from this study, not including in the artery-first group.

Reply: We agree that including A-V-A cases in the A-V group has the potential for diluting any differences between the vein-first and artery-first groups. However this classification remains appropriate (“vein-first” versus not “vein-first”) and there are many cases in which it is not possible to divide all of the arteries before the vein. Removing the A-V-A cases would eliminate 37% (106 patients) from the study, which we believe is an unacceptably high number. We believe this study still has “real world” applicability given the above.

3. They mentioned that "since robotic lobectomy is inherently a minimally invasive procedure, it is possible that minimization of tumor cell manipulation with this method therefore makes the sequence of vessel ligation not a significant factor in patient outcomes". However, I wonder how they explain the result of the following article.

Duan X, et al. Early ligation of the pulmonary vein can reduce the dissemination of shed tumor cells during thoracoscopic lobectomy. *J Thorac Cardiovasc Surg.* 2022 Dec;164(6):1623-1635.e2. doi: 10.1016/j.jtcvs.2022.03.038.

I think thoracoscopic lobectomy is also less invasive technique. If the authors really think their "robotic lobectomy" is less invasive than thoracoscopic lobectomy, they should explain what is the difference of invasiveness.

Reply: Thank you for the excellent reference. We have incorporated this into our discussion. We believe that both thoracoscopic and robotic lobectomies are excellent techniques – we do not believe that robotic lobectomy is less invasive and therefore do not need to explain this difference. The quoted text above references our comparison between robotic and *open* lobectomy, not between robotic and VATS lobectomy.

Changes: We have added the following text to the discussion: “Furthermore, a study by Duan et al suggests that the timing of vein-first ligation, early versus late, may play a role in outcomes as well. This study found that ligating the vein immediately during VATS lobectomy (early ligation group) resulted in decreased dissemination of circulating tumor cells when compared to ligating the vein later once the artery, bronchus, and pulmonary fissure were partially or completely exposed (late ligation group). This finding also introduces the possibility that even with a vein-first technique, the timing of vein ligation may also play a role in tumor cell dissemination and therefore recurrence and survival.” (page 7)

Reviewer G

I applaud the authors for performing this excellent study evaluating vein first vs artery first technique. In this retrospective study, 379 patients were identified: 95 vein-first and 284 artery-first patients. The authors found no difference in overall survival between the two groups.

I think this is a very important study that could be strengthened with either a multivariable analysis adjusting for confounding variables or a propensity score-matched analysis matching by the baseline characteristics. Can the authors also match specifically by DLCO and FEV1?

Reply: We have added FEV1 and DLCO data to Table 1. We have added a multivariable analysis (Tables 4A/4B).

Changes: Please see Table 1 for FEV1 and DLCO data. We also added the following text: “Also, patients in the V-first group appeared to have a lower mean predicted FEV1 compared to the A-first group (78 vs. 85, p=0.011).” (page 5). We have added a multivariable analysis (Tables 4A/4B).

Reviewer H

The authors examined whether there was a difference in outcomes for patients who underwent robotic lobectomy for 379 non-small cell lung cancers with venous or arterial priority and concluded that the choice of venous or arterial priority for robotic lobectomy had no significant effect on overall survival or cancer recurrence in non-small cell lung cancer patients.

The methods and results seem valid except for the limitations of this study.

I would like to make several comments as follows.

- 1) I think it would be better to properly mention NSCLC patients in the Methods ‘Study Design’.

Reply: We have added this to the study design section, to clarify that these were patients undergoing resection for non-small cell lung cancer.

Changes: Added “for non-small cell lung cancer” on page 4.

- 2) I would also need information on whether the lung cancer was completely resected or not, only for R0 or including patients with R1 and R2?

Reply: We have added this information.

Change: “The rate of R0 resection similar between both groups (V-first: 97.9% vsA-first: 98.9%, p=0.440)” (page 6).

- 3) Were data such as FEV1 and DLCO unavailable?

Reply: We have added FEV1 and DLCO data to Table 1.

Changes: Please see Table 1 for FEV1 and DLCO data. We also added the following text: “Also, patients in the V-first group appeared to have a lower mean predicted FEV1 compared to the A-first group (78 vs. 85, p=0.011).” (page 5)

- 4) It would be better to specify in the methods also what the general policy of surgery at the authors' institution was in response to the prior study. For example, was it a Vein First policy, Artery First policy, was there no specific set policy, did different surgeons have different preferences, etc.

Reply: There was no specific set policy. Surgeons divided vessels in the order that they thought was most appropriate on a case-by-case basis.

Changes: Added the following to text – “Order of division of the vessels was made at the discretion of the operating surgeon on each individual case; there was no set protocol or policy with regards to order of division of vessels” (page 4).

- 5) The difference between the number of patients at risk in the RFS and OS curves is too divergent to be normal. If this is correct, I think the reason for this should be stated clearly.

Reply: At 3 years the percentage of the original cohort that remains at risk is 19% (vein-first group) vs 25% (artery-first group), which is fairly similar. Those are the numbers of patients at risk that were obtained by our tumor registry.

- 6) To better represent the validity of the results, you should also show the results of the Cox multivariate analysis (Table) using the most important variables such as stage, age, gender, histological type, etc.

Reply: A multivariate analysis has been added (Tables 4A/4B).

7) ‘Thus, in more invasive techniques that involve greater manipulation of the lung, the sequence of vessel ligation may play a greater role in outcomes (line 150-151).’ What do you think about the degree of cancer progression, for example, tumor size?

Reply: It is difficult to speculate about the relationship between tumor size and vein-first versus artery-first technique with regards to patient outcomes. We do not believe our study is large enough to answer this kind of question.