Peer Review File

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Reviewer A: This was an observational single-center cohort study from France that included 651 patients who underwent surgical exploration for a solitary pulmonary nodule (without preop confirmed malignant/benign histology) from 2013-2019. 345 patients underwent VATS and 306 patients underwent open thoracotomy. Data were obtained from patient charts.The aim was to was to determine if a VATS approach was associated with an increased risk for lobectomy for benign lesions. The research question is interesting and clinically relevant.

Major comments:

1. Use of causal language: Avoid cause-and-effect wording such as terms like "effect," "led to" and "increased"). Instead use terms of association or correlation.

Our response: We have been careful with the terms used and have avoided cause-and-effect wording as suggested. Changes have been made throughout the manuscript.

2. It is unclear if the study was approved by an Ethics Committee or similar. Please clarify.

Our response: All patients gave their consent to participate in this study (see page 4, line 101). An opinion from the ethics committee was not initially requested because of the retrospective nature of our study. We have applied retrospectively to the committee of our French Society of Thoracic and Cardiovascular Surgery and are waiting for their opinion.

3. Because treatment allocation (VATS or open thoracotomy) was chosen by the operating surgeon and not randomized, it is possible that the two groups are not directly comparable in regards to measurable (can be accounted for) or not measurable (big problem!) factors. It may not be fair to compare outcomes (lobectomy for benign lesions) in the two groups. Indeed, Table 1 show that sex was unbalanced between the groups. There are several strategies available to address this problem, e.g., stratification or matching, but most commonly regression adjustment.

Our response: We agree that there are some biases given the retrospective nature of our study. In our institution, we usually perform VATS for clinical N0 patients with a lesion of less than 7 cm (see page 4, line 95-96). However, if the lesion is not considered resectable by VATS, the operator has the final say on the surgical approach. As there was no randomization, we agree that groups may not be comparable. The limitations of the study are mentioned on page 8, line 220-221.

4. The manuscript could be more focused. As written, there are much text (and tables) devoted to items that were not related to the aim of the study, e.g., postoperative complications.

Our response: In light of the comments made on the article, we have modified the manuscript in an attempt to make it clearer. Changes have been made throughout the manuscript.

Minor comments:

1. Line 98: Statistical analysis was not performed using RStudio. RStudio is an integrated development environment (IDE) for R. Please state what version of R statistical computing language (and non-standard packages, if any) that was used.

Our response: Statistical analysis was performed using R software version 3.5.2 and following packages were used : tidyr, epiDisplay, survival, epiR and base. This clarification has been added in the text in the "Statistical analysis" section, page 4 line 108-109.

2. Table 1: The Table can be reduced to 3 columns (merge n(%) and Mean (SD) into one column)

Our response: The table 1 has been reduced into 3 columns as suggested.

Reviewer B: The aim of this study was to compare the incidence of lobectomy for benign lesions in VATS and thoracotomy, and the authors concluded that VATS was not associated with an increase in lobectomies for benign lesions. It must be said that there are several problems with this study.

The authors mentioned that 13 patients (3.8%) in the VATS group and 8 patients (2.6%) in the thoracotomy group underwent lobectomy.
This could be considered as oversurgery, however, this number of cases was considered a little too many. Regardless of how small or deep the nodules were, could we have reduced the amount of unnecessary lung resection by performing segmentectomy instead of lobectomy?

Our response: Medical charts of patients who underwent lobectomy for a benign lesion were reviewed. The reasons why they did not undergo a wedge resection were that the lesion was considered too central or juxta scissural making a biopsy difficult. In principle, in these patients, a segmentectomy could have been performed but the vast majority of patients had a lesion at least stage IB. In case of proven cancer, segmentectomy is not recommended in a patient with normal respiratory function. The surgeon's choice was then to perform a lobectomy.

The authors also mentioned that there was no significant difference in terms of lobectomy performed for a benign lesion between VATS and thoracotomy, but in this study, the choice of thoracotomy or VATS approach was at the decision of the operating surgeon. This result

cannot regard as important, because the background of the selection of the surgical procedure was ambiguous.

Our response: The decision to perform a thoracotomy or VATS was at the discretion of the surgeon. But in our institution, we usually perform VATS for clinical N0 patients with a lesion of less than 7 cm. In these patients, a thoracotomy can be performed instead if the lesion is considered difficult to resect by VATS (suspicion of parietal pleura involvement, lesion too proximal...). This clarification has been made on page 4 line 95-96.

Reviewer C: The authors in their retrospective analysis explored if performing VATS lobectomy for indeterminate pulmonary nodules increased the need and incidence of lobectomies in case benign pathologies. This was a 6 year retrospective analysis of 651 patients of which 345 comprised of VATS cases vs 306 patients who underwent thoracotomies. The authors determined that patients who underwent VATS resection had a higher rate of non-anatomical resection of benign lesions but there was not statistically significant rate of formal lobectomies in the minimally invasive group compared to patients who undergo thoracotomy for benign lesions.

Overall: the article brings up important considerations that would be useful for the thoracic surgeons. The authors discovered that in the advent of increased lung cancer screening programs, more patients are undergoing VATS lobectomies in order to completely resect the nodules of interests for formal pathological assessment. The authors did note that those undergoing VATS who did not have pre-operative tissue assessment, do have higher rates of benign pathologies but do not seem to undergo increased rate of lobectomies compared to patients who undergo thoracotomy. The minimally invasive group do have lower complication profile.

There are couple of issues with the manuscript that could benefit from revision. The authors should ask colleagues or employ a language editing services to thoroughly read and revise the sentences. The manuscript at times are difficult to follow and understand. The authors should define the groups in the materials section, for example they use definitive pathological examination over and over which is difficult to understand.

Our response: The article has been corrected by Mrs. Debbasch, associate professor in English and specialized in scientific English. She appears in the acknowledgements section. Furthermore, we have been careful not to use certain terms too often.

Overall the article explores an important topic and this manuscript can help enrich the literature on this topic after extensive editing.

Abstract:

The abstract is slightly confusing. It is difficult to gauge why the authors chose to explore this important topic reading the abstract alone. In the introduction section's last paragraph the authors explained the reasoning why they were concerned about potential increase in formal lobectomies during minimally invasive techniques. Would suggest authors include 1-2 sentences in the introduction section on the importance of exploring the question.

27: Would suggest changing to Lung cancer screening has been associated with increase in detection of small indeterminate pulmonary nodules.

28: Sentence needs rephrasing, suggest authors to state that: In cases of inconclusive pre-operative tissue sampling, surgical resection remains the only option to make a diagnosis.

30-31: Suggest changing the second sentence and removing "from time to time"

Our response: We have tried to explain better in the abstract why we decided to conduct this study. The changes were made on page 2, line 31-34. The changes requested on lines 27, 28 and 30-31 have also been taken into account.

Introduction:

Overall the section seems short. The authors go in detail the shortcomings of pre-operative biopsies with respect to surgery but only use 1 paragraph to describe the background of VATS and need for increased lobectomies in literature. I would suggest the authors expand on the purpose of this study, their hypothesis, and expand on known current literature exploring this topic.

Our response: We have tried to enrich the introduction section with the addition of a few sentences on VATS. We also added some references on the subject. The changes were made page 3, line 70-74.

56-57: Authors should define non-surgical biopsies. Authors should also use a citation when discussing sensitivity and predictive values associated with these techniques other than CT guided biopsies as this is not the only technique involved in SPN evaluation. There are also other intra-operative adjuncts that could be cited or explored that does not involve formal resection techniques.

Intraoperative Detection and Assessment of Lung Nodules,
Surgical Oncology Clinics of North America,
Volume 29, Issue 4,
2020,

61: would suggest the authors chance the word "only" to gold standard or reliable.

64: Start a new paragraph.

Our response: We have developed the section on non-surgical biopsies. We have added the suggested reference. The changes were made page 3, line 60-64. The changes requested on lines 61 and 64 have also been taken into account.

Materials and Methods:

74: Was this a retrospective analysis of prospectively collected data or pure retrospective analysis?

78-79: remove “at least”

89: Was data analysed for 30 or 90 day hospital readmission?

98: For completeness, suggest citing for R studio, would also suggest citing the packages used for RStudio.

R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

Our response: This is a pure retrospective analysis; this has been more clearly specified in the text, page 4 line 83. Change on line 78-79 has been made. We analysed 90-day post-operative complications, this is indicated on page 4, line 98-99. The citation of the package used for RStudio has been added page 4, line 108-109 and in the references.

Results:

102: Do not need “ by the time of our study”. Suggest removing “We” or other possessives in the manuscript results section.

102-103: the sentence needs revision, what do authors mean by probable lobectomy? What do authors means by “whatever the surgical approach”.

105: Suggest changing “formed the basis of our study” to “included in final analysis”.

108: Include the numbers and not just the p values.

109: include the absolute values and not just the p values.

113: this was already stated in the previous section.

Our response: We have modified our text as advised (see page 5, line 113-123).

117-122: Shouldn't this be a table rather than Figure ?

Our response: We have changed figure 2 into a table for more clarity.

130-134: Not sure what the authors are trying to say here. This paragraph can benefit from recording and clarification

135-138: Once again not sure what this paragraph means, this is difficult to follow.

Our response: These sections have been reworded for clarity. The changes in the text were made page 6, line 142-147.

141: Do authors mean total complications, severe complications, 30 day, 90 day. This should be clarified.

Our response: We meant total 90-day post-operative complications; this has been specified on page 6, line 150.

147-148: Suggest stating the breakdown of Clavien-Dindo complications (i.e how many in each group?)

Our response: We have added in the text the proportion of grade II (see page 6 line 157-158); the rest is available in table 4.

149: What is the standard at authors institution? The length of stays for the VATS group seems very long.

Our response: The standard in our institution is a mean hospital stay of about 5-6 days. We are therefore, in the article, in our usual average.

What was the mortality, readmission rate for each group. This can help strengthen authors points if there is increased correlation with lobectomies in VATS groups with increased readmission rates and increased mortality rates.

Our response: We have added the postoperative mortality data in the results section page 6 line 160-161. These data are also available in Table 4, complications classified as Clavien grade V. We did not study the readmission rate but the rate in our institution is usually 6% at 90 days.

<u>Discussion:</u>

168-172: Sentence is long, remove " that is to say", and break down into two separate sentences.

The first paragraph should focus on authors hypothesis and how the their results and analysis fits into their hypothesis. In this case, the first paragraph is re-describing the points already raised in the introduction section.

Our response: We have totally modified the first paragraph of the discussion section to better focus on our results. The changes were made page 172-181.

184: Remove in such a way. Would suggest using Therefore.

184-185: start a new paragraph

188: unnecessary is a strong word, the surgery was necessary to evaluate a lesion that could potentially harbor a cancer.

198-199: I would argue that VATS has now become a standard and most common way lung cancer resections are performed. Would change the sentence.

I would not say that these were futile surgeries. In retrospect operating on benign lesions can seem futile but the reason these lesions were found to be non-cancerous was because of the surgery.

Our response: The changes requested on lines 168-172, 184, 185, 188 and 198-199 have been taken into account.

<u>Figures:</u>

Remove the dates from the top section on figure 1, place them in the figure legend.

Figure 2: hard to follow, increase spaces between groups or use color scheme. Suggest changing the frozen section group to confirmed by frozen section (I.e 213 patients evaluated with Frozen Section Analysis vs 132 with no frozen assessment)

Our response: We have removed the dates from the top section on figure 1 and we have changed figure 2 into a table for more clarity.

Table1: Sexe is spelled wrong. Chang to gender.
Change Smoker to current smoker.
Change "Definitive Pathological Examination" Final Histopathologic Assessment of Final Histology. The current description is confusing.

Table 3: Again change definitive pathological examination to Final Pathology.

Our response: The requested changes were made in table 1 and 3.