TRANSLATIONAL LUNG CANCER RESEARCH

Peer Review File

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Response to Reviewer A

We are grateful for your inspirational comments and constructive suggestions. We have carefully revised the manuscript. In what follows, your comments are shown in italics, which are then followed by our point-by-point responses.

General Reply: We thank you so much for your succinct summary and pointed question of our paper. We have well explained two main confusions you pointed out in the review report. They are methodological flaws and lack of oncologic outcome. The paper has been carefully revised. All the concerns (for both results and discussion) have been carefully addressed. See below for our point-by-point responses.

Reviewer A

I read with interest your paper on the usefulness of 3D printed models for anatomical sub-lobectomy. Even I really find your technique intriguing, I can not see any concrete advantage for patients. Moreover, there is no single mention on the oncological aspect of this new tool, which is mandatory in a paper discussing lung cancer. I do not agree on the outcome you measured and on the statistical methods you used. Below my comments:

1. Impressive series of patients suitable for partial lobectomy. I understand that many cases come from lung cancer screening program. Do you routinely discuss in multidisciplinary meetings the indications?

Reply 1: Thank you for your concern. We are sorry for the confusion caused by lack of final pathological results, and we have supplemented these results in Table 1. (see page 10, line 182-187) In this study, all the patients received regular follow-up chest CT scan after the first detection of the lesions. The diagnosis of lung cancer was made when the lesions enlarged or the solid component developed. All of our patients have received intensively radical segmentectomy (see page 6, line 99-100). Therefore, indications of surgery is appropriate.

As one of the largest centers of thoracic tumor surgery in China, there are more than 9,000 thoracic operations in 2019 in our center. It is unrealistic to have a multidisciplinary meeting for every patient. In fact, there is no need for regular multidisciplinary discussion in patients with early-stage lung cancer.

2. Impressive technique as well. No conversion to thoracotomy, no mortality, very few complications. No unexpected lymph node metastasis as well. Could you also

provide the results of final pathological examination?

Reply 2: Thank you for your advice. We have modified our text as suggested and provided the results of final pathological examination in the manuscript (see page 10, line 182-187).

In terms of lymphadenectomy, dissection of segmental, lobar, hilar lymph nodes in the anatomical region and sampling of mediastinal lymph nodes were performed routinely. It is not surprising that there is no unexpected lymph node metastasis. The retrospective data of our center showed that the incidence of lymph node metastasis in ground glass nodules was rare, and no lymph node metastasis was found in pure ground glass nodules. This result is similar to previous studies (1).

It is not surprising that there is no 90-day postoperative mortality, since the total postoperative mortality rate of pulmonary surgery in our center from Jan to Dec 2018 is only 0.42% (27/ 6388), let alone clinical stage I non-small cell lung cancer. Postoperative complications in this study was defined as Grade 2 or above for severe complications under the Clavien-Dindo classification system (see page 9, line 158-160), thus there are few complications reported in this paper.

Reference

1. Ye T, Deng L, Wang S, et al. Lung Adenocarcinomas Manifesting as Radiological Part-Solid Nodules Define a Special Clinical Subtype. J Thorac Oncol 2019;14(4):617-27.

3. I would not describe the case of a specific patient in methods session (lines 128-133)

Reply 3: Thanks for the careful reading. We have modified our text as advised (see Page 8, line 150-151 and Page 21, line 411-415).

Changes in the text: The case of a specific patient in methods session (lines 128-133) has been deleted.

4. Line 140: what does it mean: safety of postoperative recovery?

Reply 4: Thank you for your concern. We are sorry for the confusion. We have modified our text as advised (see Page 7, line 134-136).

Changes in the text: The extent of resection was decided by sufficient resection margin. The management of the cutting plane/intersegmental plane (electrocautery, staplers or combined application of each method) was considered relevant with postoperative comorbidities (i.e. air leak, hemoptysis).

5. How many pathological diagnosis were done before the operations and how many with frozen section?

Reply 5: Thank you for your concern. Although there are many tools for preoperative pathological diagnosis of pulmonary lesions, it is not suitable for patients with ground glass nodules to carry out invasive examination before operation. For patients with peripheral ground glass opacity (GGO) lesion considered suspicious for malignancy after the first detection of the lesions, what we have done is to give them a certain period of follow-up observation (3 to 6 months). The diagnosis of lung cancer was made when the lesions enlarged or the solid component developed. Then we assess whether these patients need surgery. Therefore, none of pathological diagnosis were done before the operations in our study.

6. There is no clear definition of complex segmentectomy

Reply 6: Thank you for your concern. We have modified our text as advised (see Page 8, line 138-141). Simple segmentectomy was defined as resection of only 1 intersegmental plane, such as lingual segmentectomy (LS4+5), whereas complex segmentectomy was defined as the resection of 2 or more intersegmental planes, such as anterior segmentectomy (S3) or combined-subsegmentectomy.

Changes in the text: APL of simple segments was defined as resection of only 1 intersegmental plane, such as lingual segmentectomy, whereas APL of complex segments was defined as the resection of 2 or more intersegmental planes, such as anterior segmentectomy or combined-subsegmentectomy.

7. You do have a very precise measurement of blood loss, up to 0.01 ml. This looks unrealistic. How do you measure the blood loss?

Reply 7: Thank you for your concern. We are sorry for the confusion caused to you. In fact, the original data of blood loss is integer. We are kindly to remind you that the reported number here is the average value of blood loss (accurate to two decimal places). Then we refer to other relevant articles and adjust the values (up to 0.1) in Table 5.

The difference between the weight of dry gauze and blood gauze plus the blood volume in the aspirator bottle is the total blood loss.

8. Also concerning the blood loss, beyond the statistical meaning of the difference between groups, there is no clinical meaning between 12 ml, 20 ml and 18 ml. This result is not informative of the outcome.

Reply 8: Thank you for your concern. We agree with the reviewer that the difference of blood loss in three groups has no clinical meaning in this study. In fact, personalized 3D printing model has its unique advantages mainly in complex segmentectomy, which is reflected in the less operative duration but not only blood

loss. In addition, the improvement of surgical technique is a complex and long process. It is difficult to fully evaluate the effect of some new techniques only according to some objective clinical values.

9. What should show a real difference for patients is the length of stay, the duration of drainage and the oncological outcome. For the latter there is no information, while for the first two outcomes there is no difference. I personally do not think that few milliliters of blood loss can make a difference in clinical practice.

Reply 9: Thank you for your concern. The indicators (length of stay, the duration of drainage and the oncological outcome) mentioned by you are mainly for the clinical outcomes of patients. We strongly agree with this comment, however, this is a partial view for surgery. The operation itself cannot be ignored. As mentioned in the introduction section, surgical treatment of early-stage NSCLC is various. How to complete a successful operation is a challenge to surgeons. The intraoperative indicators, such as operative duration or blood loss, are significant factors for successful operations. In addition, subjective evaluation of new technology by surgeons is also an important indicator in clinical practice. 3D reconstruction imaging and 3D printed model both have significant advantages in locating nodules and identifying vascular variations. Personalized 3D printed model then enhanced the confidence of surgeons to make decisions and perform complex surgery. This explains why there are more complex segmentectomy in 3D model group.

10. You often mention the costs of the procedure, but you never give any information.

Reply 10: Thank you for your concern. Printing a personalized 3D model for a patient costs about 3,000 RMB. For most patients, it is affordable and effective.

11. What do you exactly mean with "patients have the right to choose 3D model"? Do patients pay for having this tool available during the surgery?

Reply 11: Yes, patients need to pay for 3D model. So, patients have the right to choose 3D models. But for most patients who were recommended by surgeons to print a model, they are willing to pay for it after communication. Most Chinese hospitals didn't have 3D printing machine yet. We authorized third-party companies to print the model. Now, some provinces in mainland China, including Beijing, are planning to incorporate 3D printing models into health insurance policies. We believe that in the near future we will be able to print models for appropriate patients with no limitations.

Changes in the text: However, not all patients are willing to choose to spend some

money to have 3D printed models voluntarily, it is challenging to perform prospective controlled studies. (See page 12, line 236-237)

12. If it is a voluntary choice, when do they decide?
I guess you have a meeting with patient to explain the need and advantages of this tool, to show them its usefulness and collect the agreement for expenses. If this is the case, in which moment do you find the 3D model useful for counselling? Do you discuss expenses prior to medical counselling? This is very confusing.
Reply 12: Thank you for your concern. We are sorry for the confusion. There is no doubt that we are willing to prepare 3D models for all anatomical partial-lobectomy without considering the economic cost. But that is far from the case. Thus, Table 5 showed a relevant reasonable strategy for doctors selecting appropriate early-stage NSCLC patients to print 3D model. In fact, if a personalized 3D model was helpful to the surgery, we would talk to patients and explain the usefulness of 3D model. This counselling was completed on the first day of admission. We routinely tell patients how much they need to pay for this 3D model as counselling. In our experience, most patients were not bothered by the extra costs.

13. The main and not ignorable limitation of the study is the statistical analysis. There is no mention on normal distribution check; therefore, there is no knowledge of tests appropriateness. Moreover, it is unlikely that all the variables were normal (age, fev1, diameter of the lesions and so on), thus, the display of the variable is not correct. Additionally, pairwise comparison must be corrected for multiple testing if groups are more than 2
Reply 13: Thank you for your concern. Firstly, according to your suggestion, we have done normal distribution check for all the variables. The P values of the KS statistic for the variables are: Age ($p=0.062$), FVC ($p=0.2$), FEV_1 ($p=0.012$), Lesion diameter ($p=0.12$), operation duration ($p<0.01$). For those variables that didn't pass the normal distribution test, we have checked their Q-Q plot, and find only a slight skewness exist. We do believe that these variables are appropriate for ANOVA analysis. We think the current display of the variables is suitable since they are normal distributed or slightly skewness. If we are wrong, please point us a better way to display them, and we will very appreciate it. Finally, thank you for your concerns about the multiple testing problem. We adopt ANOVA analysis since the group number is 3.
Changes in the text: The measurement data were expressed by "mean± standard deviation (±SD)", and ANOVA analysis was used for comparison when groups are more than two. The number of cases (n) was used to express the counting data, and the $\chi 2$ test was used to compare the rate of counting data between groups (%). (see

Page 9, line 166-169)

14. Tables are very difficult to read. In table 1, in the variable named "complications" there are some medical conditions that, I suppose, are comorbidities.

Reply 14: Thank you for your concern. We have modified our table as advised (see table 1).

15. Language review looks mandatory

Reply 15: Thank you very much for this suggestion. In this revision, we have rewritten the manuscript, so that the paper can be better read. To improve the writing, we first polish the English many times. Moreover, we hired a professional English editing service to further polish the English, so that the writing can be improved.

16. I do not find acceptable to submit a paper on "stage I lung cancer" without a single mention on histology and pathological staging and oncologic outcome

Reply 16: We thank you so much for this critical comment. We do find this comment is valid and extremely helpful, and this defect have been carefully addressed. The results of final pathological examination and staging have been added to the manuscript (see page 10, line 182-187).

Response to Reviewer B

We are grateful for your inspirational comments and constructive suggestions. We have carefully revised the manuscript. In what follows, your comments are shown in italics, which are then followed by our point-by-point responses.

General Reply: We thank you so much for your very precise and succinct summary of our paper. All the points to discuss have been carefully explained. See below for our point-by-point responses.

Reviewer B

Dear authors,

Thank you for giving me the opportunity to review your study.

You evaluated the utility of 3D printing for VATS segmentectomy in a large series of patients over a short period of time.

Your article is interesting and well-written.

Several points to discuss:

- Do you consider the reconstruction, not only for anatomy but also for margin resection? It would have been interesting to differentiate peripheral and central

lesion in your manuscript.

Reply 1: Thanks for your advice. We quite agree with your view. In fact, the most important advantage of 3D reconstruction is preoperative planning. As we written in discussion section (see page 13, line 260-261), 3D reconstruction imaging can accurately locate pulmonary nodules and target segments. Here, to design margin or intersegmental line before operation by using 3D reconstruction is a critical step in anatomical partial-lobectomy (APL). We have been revised discussion section, presented this application value of 3D reconstruction.

In addition, you suggest that differentiate peripheral and central lesions. It's a wonderful idea. But in our study, most focus of lesions located in middle or lateral zone of the lung. For central lesions, it is difficult to perform a standard segmentectomy in practice. Based on these reasons, it may not be reasonable to divide peripheral and central lesions in this study. Inspired by this comment, we can write a paper to describe APL for central lesions

- I didn't understand how you selected 3D printing vs no printing? Was it based on the personal preference of the surgeon?

Reply 2: Thank you for your concern. We are sorry for the confusion caused to you. Now, there is no current recommendation or consensus on selecting appropriated early-stage NSCLC patients for 3D reconstruction or 3D printing model in China. When the surgeon needed a 3D model to guide operation, the case would be discussed in the surgeon's medical group and to decide whether to prepare a 3D model for the patient. In this study, after a live meeting discussion, we propose a preliminary score criterion for reference (Table 5). In the near future, we may select 3D model based on a more effective strategy.

> ***- Another important aspect is the prize. What does it cost? Because first the software for 3D reconstruction is quite expensive and I suppose the 3D printing as well! It would have been interesting to have an idea of the additional prize per procedure. Does this prize justify the low rate of clinical advantage?***

Reply 3: Thank you for your concern. Any new technologies may be expensive in the primary stage of application. A typical example is robotic surgery. Now, in our center, patient only need to pay about 3,000 RMB for a personalized 3D model. It's pretty cheap for most Chinese patients. The cost of this model is only about 4% (3000/70000 RMB) of the total cost during hospitalization. This prize did not decrease its clinical advantage, on the contrary, reasonable charges reflect its clinical value. There is no doubt that the development of 3D technology will also reduce the cost and expense of 3D model.

- How do you print the reconstruction? Did the hospital buy the machine? You explained that it is long (8 to 15h!)

Reply 4: Thank you for your concern. Our center don't buy the machine. We only buy the 3D reconstruction software and then authorized third-party companies to print the model. The company could send 3D model to patients within 24 hours.

- You have many surgeons performing the procedures (almost 50). It would have been interesting to differentiate staff from fellow or students.

Reply 5: Thanks for your advice. There may be some misunderstandings. A total of 59 surgeons who completed the questionnaire come from different hospitals in China. They all used and interested in 3D technology, and attend the meeting hold by our center. In this study, the operations were all performed by experienced surgeons in our center, which can ensure the uniformity of operation quality.