

Peer review file

Article information: <http://dx.doi.org/10.21037/jtd-20-1448>

Reviewer A

Comment 1: As the author pointed out, 2 of the 10 cases with poor efficacy were cases of emphysema. In order to deepen the reader's understanding more concretely, (Table 1) should be described separately for "Patient characteristics" and "Operative procedure" (e.g. Operative results, etc.)

In "Patient characteristics," please add information on smoking history, the degree of smoking (e.g. packs-years, or smoking index, etc), pulmonary function, comorbidity, TNM, tumor diameter, solid or not solid, and the location of the tumor.

Please add blood loss, additional sealing (e.g. fibrin glue, PGA seat, etc.), and the degree of visualization of the intersegmental plane using PDE-neo to "Operative procedure (results)".

Reply 1: In accordance to your suggestion, we separated Table 1 into two tables: "Patient characteristics" and "Operative result". The factors you specified were added to the tables.

Changes in the text: Table 1, 2

Comment 2: Two cases of pneumonia were reported in the Complications section. Is this pneumonia at the site of the remaining pulmonary segment?

Reply 2: Pneumonia occurred in a different lobe from the remaining pulmonary segment.

Changes in the text: Lines 168–169

Comment 3: Is PDE-neo unique compared to other fluorescence detectors? Is it possible to use other fluorescence detectors to visualize intersegmental planes by the same procedure?

Reply 3: It is possible to identify intersegmental planes with other fluorescence detectors as well as with PDE-neo.

Comment 4: How did the air leak occur from the surface of resected segmental parenchyma?

Reply 4: There was a mild air leak from the area surface separated by the electric knife. However, control was possible using soft coagulation, PGA sheets, and fibrin glue.

Changes in the text: Lines 163–164, Table 2

Comment 5: How far was the distance from the tumor to the segmental cutting margin? Were there any criteria for determining the margin to perform pulmonary segmentectomy?

Reply 5: We made a surgical plan to have a margin equal to or larger than the tumor diameter.

Changes in the text: Lines 107–108

Comment 6: About the configuration

Line 131-Please describe “Results and Conclusions” by dividing them into “Results”, “Discussion”, and “Conclusion”.

Please add a method for dealing with cases of poor visualization of intersegmental plane that you experienced this time to “Discussion” and also consider referring to the literature.

Reply 6: "Results and conclusions" were divided into "Results," "Discussion," and "Conclusions". We added a method for dealing with cases of poor visualization of intersegmental plane. Reference 12 was added as well.

Changes in the text: Line 160–162

Comment 7: Line91 Please describe the specifications of PDE-neo. Please add size, morphology, and method used in thoracoscopic surgery.

Reply 7: We described the specifications of PDE-neo.

Changes in the text: Figure 1, Lines 100–102

Comment 8: Line123 “a mixture of ICG and autologous blood was introduced”. Please describe the amount of ICG used and the amount of autologous blood used.

If you have a rationale for the amount used, please cite the literature.

If you have a rationale for using blood in the admixture, cite the literature.

Reply 8: We have added this description to the revised text. Sekine et al. (Reference 11) used 5-fold saline-diluted ICG, but we used 5 ml each of ICG and autologous blood that was more visible in PDE. As I wrote in Line 73–75, ICG emits the near-infrared light by binding with $\alpha 1$ lipoprotein in the blood (Reference 6).

Changes in the text: Lines 127–130, Figure 3

Comment 9: If ICG is absorbed by the tissue after spraying and the amount of fluorescence detected is reduced, how long is it effective during surgery? Is its efficacy

related to the amount used or the volume of the excised area?

Is there any influence on the pathological inspection and diagnosis?

Reply 9: We do not have that data because we haven't measured how long the fluorescence lasts. The use of ICG had no effect on pathological diagnosis.

Changes in the text: Line 141

Comment 10: Line141 “right S2 + S3 segment (anteroposterior segment of the upper lobe)”

→ In Table 1, it is written as right S1 + S2. Clarification is needed.

Reply: Thank you for pointing out this mistake. S2 + 3 is correct.

Changes in the text: We modified Table 2

Comment 11: Line143 “1 left basal segment” → Table 1 lists two cases. Clarification is needed.

Reply 11: Thank you for pointing out this mistake. Table 1 is correct and left basal segment were 2 cases.

Change in the text: Line 148

Comment 12: Line152 “There were no complications resulting from ICG angiography”

→ Isn't “transbronchial administration” correct rather than the ICG angiography?

Reply: As you pointed out, “transbronchial administration” is correct.

Changes in the text: Line 156

Comment 13: Line153 “those of 2 cases could not be identified.”

Could segmentectomy not be achieved in these two cases?

How was the segmental resection completed?

Knowing this will be helpful information for troubleshooting when the reader performs the same procedure.

Reply: In these cases, pulmonary emphysema was so severe that the air inflation technique could not be used, so an incision was made between the anatomical segmental planes separated by the pulmonary veins.

Changes in the text: Lines 160–163. We also added reference 12.

Comment 14: Line189 "However, a method has been reported in which ICG is intravenously administered and the area is identified using an infrared thoroscopic

system (13).”

This sentence seems mistaken.

Sekine et al. have reported surgical results with injecting the ICG mixture into the segmental bronchus using the PDE as was used to perform the segmentectomy mentioned in this paper.

Reply 14: Thank you for pointing out this mistake. This was a mistake in Reference 8, not Reference 13.

Changes in the text: Revised citations to 8 (Line 211), and (13) was deleted (Line 212).

Comment 15: Line219 Add “.” In the sentence.

Reply 15: We have added a “.”

Changes in the text: Line 219

Comment 16: Please prepare “Figure legends”.

Reply 16: In the manuscript I submitted, I added “Figure legends” separately. However, in the manuscript for the reviewer, it is no longer double-spaced and the figure legend is gone. This was a problem of the editorial process.

Comment 17: Figure 1 Please specify which case in Table 1 and the name of the segmental bronchus injected and the lung segment.

Reply 17: We added the case number (case 2) and other information.

Changes in the text: Figure legend for Figure 2 (Lines 340–343).

Comment 18: Figure 2 Please show the fluorescence image in comparison with the macroscopic findings, and specify which case in Table 1.

If possible, please provide a photograph of the deep-cut section of the segmental plane that can be identified by fluorescence.

“displayedin white” -> “displayed in white” ?

Reply 18: We corrected the explanation in Figure 4 to "displayed in white"

Changes in the text: Lines 346–347

Comment 19: Figure 3, 4 Please change the unit of the horizontal axis to month.

In Line163, median follow-up period is indicated by month.

Please add "No. at risk".

Reply 19: We changed the unit of the horizontal axis to “month” in Figures 5 and 6. Since the survival curve is for 10 cases, the cases can be identified by censoring and

reduction in survival rate. Therefore, I think "No. at risk" is obvious and unnecessary.
Changes in the text: Figures 5 and 6.

Reviewer B

Comment 1: the population of the study is small: follow-up and survival data should be descriptive, and this limitation should be highlighted properly.

Reply 1: What you have pointed out is described in lines 236–239 of the text.

Comment 2: English language can be improved.

Reply 2: This manuscript has been edited and proofread to ensure that the language is clear and free of errors by professional editors. Please indicate which part of the text in English needs improvement.

Reviewer C

Comment: 1: In line 105/106 you mention that 9 patients underwent segmental resection via passive reduction surgery owing to poor lung function and complications – could you define passive reduction surgery and what complications are you referring too?

Reply 1: "Passive reduction surgery" was performed for patients who cannot tolerate a lobectomy.

Changes in the text: Line 143

Comment 2: Were the cases performed open or minimally invasive?

Reply 2: We performed lung resection with combined muscle-sparing minithoracotomy and video assistance.

Changes in the text: Lines 122–123

Comment 3: Can you explain how you accessed the divided airway for instillation of the ICG-blood mixture? How as the mixture aerosolized and administered? How did you ensure its delivery? Does the segment inflate during ICG administration? How much volume and what ratio of blood to ICG was used?

Reply 3: The answers to the first four of your questions are detailed in “Operative Technique” (lines 124–130).

Changes in the text: Line 127–128

Comment 4: Why use airway anatomy to determine intersegmental planes? Can there be collateral ventilation from neighboring segments that could skew your results? A similar technique is used with daVinci system where ICG is injected intravenously after division of the vascular supply – the segment of interest then becomes the only portion of lung to not enhance on infrared. Could you speculate on which of the two methods may be more accurate in terms of segment planes?

Reply 4: Since we developed this method by improving the air inflation technique (Reference 4, 5) and Oh's report (Reference 14), we adopted intra-bronchial injection. This is written in detail in Lines 201–203.

Because traditional segmentectomy was based on bronchial anatomy and the lymphatic channels from the tumor are along the bronchi, we believe that transbronchial introduction of the ICG is ideal. However, it is not important whether intrabronchial infusion or intravenous infusion is better; it is of utmost importance to make the best use of the merits of both to identify the areas correctly.

Changes in the text: Lines 213–219 were added.

Comment 5: Line 152 you mention “angiography” – is this the correct term? ICG is not being injected into the vessels?

Reply 5: As you pointed out, “transbronchial administration” is correct.

Changes in the text: Line 156

Comment 6: Could you report your surgical margins?

Reply 6: We made a surgical plan to have a margin equal to or larger than the tumor diameter, and the surgical margin was negative in all cases.

Changes in the text: Lines 107–108

Comment 7: This technique failed to demonstrate the planes in 2 patients due to emphysema– that’s a 20% failure rate. What can be done to improve this technique?

Reply 7: Like the air inflation technique and Oh's report, the weak point of this method is emphysema lung. The failure rate changes depending on the proportion of severe emphysema cases, but we think a success rate of 80% is acceptable.

Comment 8: Do you think the post-op complications (pneumonia and wound infection) are related to the ICG technique?

Reply 8: We think that pneumonia and wound infection is not a complication associated with the ICG technique.

Comment 9: Higher quality pictures are needed to see the technique – a video would be even better to illustrate this technique.

Reply 9: We changed the Figure 4 to higher quality pictures.

Reviewer D

Comment 1: New techniques such as thoracoscopic segmentectomy using intravenous ICG combined with ICG-VAL-MAP have been reported by some authors these days. The authors should comment about future perspectives with those new appearing techniques.

Reply 1: We have a statement addressing this into the discussion.

Changes in the text: Lines 219–225

Comment 2: I am afraid that this method is not so effective as intravenous ICG administration is due to the following issues: 1) the risk of pneumonia caused by intrabronchial administration can occur. 2) The ischemia area is more harmful than the unventilated area. So, intravenous ICG administration is more reasonable for identification of segmental planes.

Reply 2: Since the ICG is injected into the area to be surgically excised, the risk of pneumonia due to ICG does not matter. The question being asked has the premise that the ischemic lung remains in the remaining lung, but this is not so. Since the appropriate pulmonary veins and arteries were separated before ICG injection, the ischemic area can be visually identified. In fact, there are no complications.

Comment 3: I would like to know if the authors keep conducting the technique and the reasons why.

Reply 3: We performed lung resection with combined muscle-sparing minithoracotomy and video assistance (Line 122–123). We do not use this method in thoracoscopic surgery because it is somewhat difficult to inject ICG into the bronchus under complete thoracoscopic surgery. However, open surgery uses this method instead of the air inflation technique.

Comment 4: The authors should comment about future perspectives against severe emphysema.

Reply 4: We have added text to the discussion.

Changes in the text: Lines 215–224

Comment 5: The words “5-year corrected survival rate (line 45)” seems to be relatively uncertain.

Reply 5: "5-year corrected survival" is a mistake of "5-year cause-specific survival".

Changes in the text: We corrected Line 47

Comment 6: The Results, Discussion, and Conclusion sections are to be separated.

Reply 6: "Results and conclusions" have been divided into "Results," "Discussion," and "Conclusions".

Comment 7: Figure 2 is unclear. An easy-to-understand video is preferable.

Reply 7: We changed the Figure 4 to higher quality pictures.

Reviewer E

Comment 1: The authors mentioned that “segmentectomy is performed based on bronchial anatomy, and transbronchial introduction of ICG is ideal”. In my opinion, however, surgical margins from the tumor are important in segmentectomy for malignancy. How do you secure the surgical margins in your method?

Reply 1: We made a surgical plan to have a margin equal to or larger than the tumor diameter. That is, only cases in which the margin from the segmental plane to the tumor was equal to or larger than the tumor diameter were included in this study.

Changes in the text: Lines 107–108, 226–227

Comment 2: You mentioned that most of ICG fluorescence usages are performed by intravenous administration. What are the real merits or strengths of your method over intravenous administration?

Reply 2: Traditionally, segmentectomy has been performed based on bronchial anatomy. In addition, the lymphatic channels from the tumor are along the bronchi. Therefore, we believe that segmentectomy using transbronchial introduction of ICG is ideal.

Changes in the text: We added Lines 213–216

Comment 3: You also mentioned that in 2 cases, intersegmental planes could not be identified due to the sever emphysema. It is also observed in the conventional residual

segment expansion method. Conversely, it can be said that conventional method allows intersegmental planes to be visualized similarly with your technique. Furthermore, conventional residual segment expansion method with jet-ventilation probably allows intersegmental planes to be more clearly visualized. What are strengths of your methods over the conventional techniques?

Reply 3: Although the inflation/deflation technique is effective in identifying the demarcation line on the pleural surface, it is ineffective for deep parts of the lung. Our method is effective for deep parts of the lung.

Changes in the text: We added this to Line 157

Comment 4: The conclusion that “this method has a good long-term prognosis” should be deleted because there are no relations between this method and prognoses of patients.

Reply 4: LCSG reports that limited resection has three times the risk of local recurrence compared to lobectomy. In segmentectomy, it is important to have a sufficient resection margin, and it is necessary to recognize correctly the segment plane during surgery. The fact that one recurrence case was not recognized by this method shows that the segment plane was correctly identified and segmentectomy was performed. So, there is a relationship between this method and prognoses of patients.

Changes in the text: We added text to the discussion (Lines 226–235).