

Peer Review File

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Reviewer A

I would like to congratulate you for your study and effort. This is a very nice retrospective anatomical study to identify anatomical variation of the segment 6 of the RLL. Your results showed that anatomical variation was present in substantial number of cases. These results highlight the importance of planning and anatomical knowledge before segmentectomy in order to avoid intra-operative problems. My only concern is that in my experience the anatomical variation can be identified with the lecture of the CT-scan on 2D...

Did you try to identify the anatomical variation by CT only without 3D reconstruction. Do you really think that 3D reconstruction can offer more information than a good lecture of CT-scan... Otherwise congratulations for effort.

Reply A: Thank you for your questions. As you mentioned, the role of 2DCT cannot be ignored. I personally tried to analyze and find these anatomical variations directly through 2DCT, and the results showed that 5 cases of B6 bronchial variations could be found from 2DCT, while about 5% of arterial and venous variations could not be found from 2DCT. Personally, I have been engaged in the specialty of thoracic surgery for more than 10 years. In my opinion, finding anatomical variation through 2DCT depends on the clinical experience and level of physicians. There is a big difference between physicians with different years of experience, so they are not friendly to young physicians and have a long learning curve. 3D reconstruction can intuitively present this anatomical variation, narrowing the level of film reading between junior and senior physicians, and combining 2DCT with 3D reconstruction is more conducive to the growth of physicians. We will analyze the anatomical structure of the target segment and adjacent lung segment from 3D reconstruction, as well as the bronchi and blood vessels involved in the 2cm safe incision margin, and then make dynamic and stereoscopic analysis to formulate the surgical plan.

Changes in the text: None.

Reviewer B

The authors are demonstrating the complexity of the segment 6.

I have some remarks:

1. Would the authors recommend 3D-CTBA in all patients they are operating on a nodule of segment 6 or just in case of centrally located nodules?
2. Were some anatomic variants already been seen in the ct-scan? Have the authors analyzed this?

3. How much were the costs for 3D-CTBA analysis?

4. From my point of view, a percentage of the anatomical variant should be indicated on the figures.

Reply B1:

Thank you for your questions. Yes, we recommend routinely use 3D-CTBA for all patients which are scheduled for segmental resection. Our self-developed software (DeepInsight) takes only about 5 minutes to complete 3D imaging from importing Dicom picturesdata, which is convenient for application.

Changes in the text: None.

Reply B2:

Thank you for your questions. We tried to analyze these anatomic variations found by 2DCT, and the results showed that 5 cases of B6 bronchial variation could be found by 2DCT, while about 5% of arterial and venous variation could not be found by 2DCT. In my opinion, finding anatomic variation through 2DCT depends on the clinical experience and level of the physician, and there are great differences among physicians with different years of experience. Three-dimensional reconstruction can intuitively present this anatomical variation, narrowing the level of film reading between junior doctors and senior doctors, shortening the learning curve of young doctors, and more conducive to the growth of doctors.

Changes in the text: None.

Reply B3:

3D-CTBA analysis costs 970RMB/per patient, which is covered by Medicare.

Changes in the text: None.

Reply B4:

Thank you for your questions. In order to avoid compromising the quality of the image, we have added the percentage of anatomical variation in the comments below.

Changes in the text: see Page 17, line 456; Page 18, line 460-461,470-471.

Reviewer C

I congratulate the authors for performing an outstanding study evaluating the intricacies of the S6 artery. This series will be very informative for thoracic surgeons.

Reply C: Thank you for your encouragement.

Changes in the text: None.

Reviewer D

I would like to thank the editor and authors for providing me with a great opportunity to review such a valuable article. This manuscript focused on branching patterns of bronchus and vessels of right segment 6. I have several comments.

1. Regarding Table 2, the rate of A6 arising as three separate stems was approximately 10 %. This would be highly different than previous reports. I was amazed by this rate because I have hardly observed A6 arising as three separate stems. I would like to know the reason for discrepancy. Was it because of ethnic difference? Authors should address this issue.

Reply D1: Thank you for your questions. We reanalysed CT and 3DCT of all cases arising as two separate stems from B⁶. As you pointed out, B^{6c} in some cases was indeed confused with B* as defined by Boyden, Shiozawa and Yamashita, and the incidence of 2 stems was 3.48%. We have modified the data of B⁶ and A⁶, and the classification of V⁶ is not affected. This study is a single-center retrospective study mainly aimed at the Chinese population. Such results may be related to selection bias caused by the small sample size we selected.

Changes in the text: see Page 15, line 433-434.

2. In line 76, authors said "co-dry". Does "co-dry" make sense? Or is it a typo? Authors should confirm.

Reply D2: Thank you for your questions. To avoid confusion for readers, we have changed "V⁶ and V⁸⁺⁹ co-dry" to "co-draining of V⁶ and V⁸⁺⁹".

Changes in the text: see Page 4, line 77.

3. If authors wanted to state that variations were much common than previous reports, they should perform statistical analyses. Table 1,2 and 4 suggested comparisons of their data and previous data. They should calculate p-value and confirm that their data had truly been different from other reports.

Reply D3: Thank you for your questions. We re-compared the previous data analyzed with our own data and calculated the P-value. The results are shown in Tables 1, 2, and 4.

Changes in the text: see Page 15, line 439-440, Page 16, line 442-443; Page 16, line449-450.

4. I think that this manuscript would be important, however a lit bit boring because the article only displayed a data. I could not see the value of this paper. Authors should clarify the usefulness of the current paper.

Reply D4: Thank you for your questions. The results of JCOG0802 and CALGB140503 have increased the clinical demand for segmental resection in the treatment of early lung cancer. However, the lung segment dissection is complicated and the frequency of variation is high, and the technique of lung segment resection is difficult. S⁶ resection is considered to be the simplest lung segment surgery. In recent years, no clinical experts have conducted anatomical or imaging analysis of S⁶ and explored the clinical significance of bronchial and vascular variation. As you know, S⁶ excision can be very difficult if B⁶ is double branched, A⁶ and Asc.A² are co-dry, or V² is regressing to V⁶ with oblique infissure or fusion. At this time, if there is three-dimensional guidance, the variation of the anatomical structure will be understood, and the non-target segment structure or residual target segment structure will be avoided during

the operation. In addition, S⁶ is adjacent to S⁸, S⁹, and S¹⁰, and if the nodule location is deep and close to V^{6b} or V^{6c}, the safe margin cannot be guaranteed after S⁶ resection, which leads to a high local and global recurrence rate. Nakazawa et al. believed that the poor effect of excision of the upper segment of the right lower lung was due to the problem of intersegment plane clipping. We believe that for deep nodules close to the intersegment, the best surgical option is S⁶ plus one or two adjacent subsegments.

Changes in the text: None.

5. Regarding Figure 2B, I assume that A6c may be A※ (subsuperior segment). Subsuperior segmental branch may sometimes be confused with a branch of A6. How do you distinguish them? The extremely high rate of A6 branching into three separate stems may be due to misunderstanding of subsuperior segmental branch. Authors must address this issue.

Reply D5: Thank you for your questions. S* was first defined and named by Boyden in 1945. S* was identified according to its bronchus (B*), which was defined as a separate bronchus originating from the basal or secondary basal trunk bronchus. Notably, the structure of the S6 must be complete. Why is this Figure 2B not A*? Because there is no independent bronchial B*, this artery is concomitantly with B6c, so it is considered to be A6c. Second, the simple way to identify A⁶ and A* is that the one above V⁶ is A⁶.

Changes in the text: None.

Reviewer E

1. General remarks

The authors investigated to assess determine the patterns and variations of the bronchus and blood vessels of the superior segment of the right lower lobe (RS6) using three-dimensional computed tomographic bronchography and angiography (3D-CTBA) reconstruction. This study suggests that it is crucial for readers to use 3D CTBA and plan the surgery well in advance when performing RS6 segmentectomy or right lower lobe segmentectomy including S6. However, I have some concerns about this study.

2. Specific Comments

a) Major

I) Page 4 lines 59-61 and 79-80 in Abstract session

The background abstract states that the purpose of this study is to explore the clinical significance of right S6 resection, but there is no discussion of this. Rather, it is difficult to explore the significance of right S6 resection cases because this study does not address clinical outcomes such as the presence of local recurrence or truncation. This study only clarified the bronchial and vascular branching patterns, and it is difficult to conclude whether it was useful or not; studies are needed to determine how the presence or absence of 3D-CTBA affects the postoperative outcome of right S6 segmentectomy. What are the authors' thoughts?

Reply E a: Thank you very much for the reviewer's comments. The core of this study is

anatomic variation and its impact on surgery. Therefore, the possible reasons for poor prognosis of lung cancer in the upper right lower lung segment were discussed from the perspectives of anatomic variation, surgery and incisal margin size. We have modified the Background according to your comments. Your comments provide a good idea for our next research plan. Changes in the text: see Page 4, line 60-61.

b) Minor

I) Page 7 lines 162-171 in Results session

It might be easier for readers to understand if there is a table as patient characteristics.

Reply E b I: Thank you for your questions. We briefly described the characteristics of the patients in the first paragraph of the results. Due to the limitation of space, we did not make a separate table. We will provide this form in the supplementary agreement.

Changes in the text: None.

II) Page 9 lines 236-237 in discussion session

I think that the dominant pattern of the bronchus B6 was single-stem bifurcated 2 branches type is probably an 89.2% error.

Reply E b II: Thank you for your questions. We have verified the relevant data again and revised the article.

Changes in the text: see Page 10, line 260.

III) Page 9 lines 252-253 in discussion session

I think that a period is missing in the next sentence.

“Co-stem with A2 was the most frequent variation form of A6 (n=25, 7.9%)”

Reply E b III: Thank you for your questions. We have added a period after this sentence.

Changes in the text: see Page 10, line 277.

IV) Page 10 lines 261-263 in discussion session

I think that the number in the next sentence is incorrect; it should be 94.3%, not 64.6%.

“V6 was classified into 7 patterns in the current study, and consistent with the Yamashita report, single-stem bifurcation was the most common pattern (64.6%).”

Reply E b IV: Thank you for your questions. We state that the V6 single-stem incidence is 94.3%, including single-stem splitting into two branches (64.6%) and single-stem splitting into three branches (29.7%).

Changes in the text: None.

V) Page 14 table 1

I think it would be easier for the reader to understand if the table 1 showed the numbers and not just the percentages.

Reply E b V: Thank you for your questions. We have made appropriate modifications to Table

I and added the comparison of P-values, which I think is more conducive to readers' understanding.

Changes in the text: see Page15, line439-440.

VI) Page 16 Figure 2 and 3

In Figure 2 and 3, is the X in AX6, VX2, etc. a misdescription? Or does it have some meaning? If so, please add an explanation of the X in Figure legends.

Reply E b VI: Thank you for your questions. According to the bronchial and blood vessel nomenclature described by Boyden in 1946, the letter "X" first appeared, and the structure derived from adjacent lung segments or subsegments in the position of normal lung segments or subsegments was named "X", indicating abnormal co-trunk. We added an explanation of the "X" in the comment.

Changes in the text: see Page18, line462-465; Page18, line473-476.

VII) Page 17 Figure 4

The colors of b and d in Figure 4 are confusing. Please correct it for clarity.

Reply E b VII: Thank you for your questions. In Figure 4, b and d are because we adopted different reconstruction strategies to highlight the lung volume and appropriate incisal margin, and appropriately added colors just to highlight the incisal margin position.

Changes in the text: None.

Reviewer F

This paper is a study that evaluate the branching patterns of segmental bronchus and blood vessels in the superior segment of the right lower lobe using 3D-CT. However, there are a several problems with this manuscript, some of which need to be revise/rediscuss as follows.

Introduction:

#1 line 93-108

Since the content of this section overlaps with DISCUSSION, it would be better to change one of them to be less repetitive.

Reply F #1: Thank you for your questions. We have revised the discussion section.

Changes in the text: see Page11, line310-316.

Methods:

#2 Clinical data and 3D-CTBA reconstruction

Could you please provide a little more detail on the contrast CT protocol you performed, including contrast injection rate?

Reply F #2: Thank you for your questions. We have added some details of the CT scanning protocol to the article.

Changes in the text: see Page6, line130-134.

RESULTS:

#3 line 163-167

Please describe the details of the subsegmental resection.

Reply F #3: Thank you for your questions. We have added some subsegment excision details to the method.

Changes in the text: see Page6, line144-150.

#4 line 183-219

The table overlaps with the description in the RESULT regarding the branching pattern of the bronchus, pulmonary artery, and pulmonary vein. Please summarize the information in a table in an easy-to-read format and only include in the text what is necessary that cannot be included in the table.

Reply F #4: Thank you for your questions. We have made appropriate changes to the results section.

Changes in the text: see Page8, line194-199.

#5 line 183-187

You mentioned "B6 had either a single (n=282, 89.2%) or 2 stems (n=34, 10.8%)." However, is it really 2 stems? Could the caudal bronchus be a B* that Yamashita described? How did you handle the B*? If it is B*, it would be different from how A6 or V6 also divides the branching pattern. Could you please reconsider this?

Reply F #5: Thank you for your questions. S* was called "the second dorsal hyperarterial bronchus" by Aeby (1880), "the lesser posterior horizontal bronchus" by Ewart (1889), the "subapical branch" by Hardie-Neil and Brock, the "subsuperior or suprabasal branch" by Jackson and Huber, and the "subsuperior branch" and represented by an asterisk by Boyden, i.e., B*, which is further divided into a lateral ramus, a, and a posterior ramus, b.

According to the definition of Aeby, Ewart and Hardie-Neil, the anatomical position of S* is horizontal, posterior to the region between the superior and basal segments of the lower lobe. The definitions of Boyden and Yamashita described S* in the posterior part of the right lower lobe, while for the left lower lobe, Boyden defined it to be in the posterolateral position, and Yamashita stated it is in the lateroposterior part. In 1946, Brock proposed "to restrict the name subapical (i.e., subsuperior) to the one in constant but commonest posterior bronchus, and to name and describe any others separately". Oho and Amemiya found that the bronchus of S* is also in the posterior position under bronchofibroscope examination. Because the anatomical nomenclature of lobes, pulmonary segments, and subsegments is based on their actual anatomical positions in the thoracic cavity, and based on the facts of classical anatomical definition of the position of the S* bronchus, which was also supported by bronchofibrosopic examination findings, we think the definition of S* bronchus given by

Brock is more legitimate and therefore propose to define the S* bronchus as the one situated between the superior and basal segmental bronchi (i.e., between B7 and B9+10 or between B7 and B10) and originates from the stem bronchus of the basal segment. At the same time, it is limited to the bronchus with its orientation pointing to the posterior direction in the right lower lobe, and to the posterolateral direction in the left lower lobe. The space occupied by the S* will not reach the diaphragmic surface of the lung. The nomenclatures of bronchi in other regions between the bronchi of superior and basal segments are given according to their anatomical positions in the thoracic cavity as BX (for example, BX7b, BX8a, BX9a). We reanalysed CT and 3DCT of all cases arising as two separate stems from B⁶. As you pointed out, B^{6c} in some cases was indeed confused with B* as defined by Boyden, Shiozawa and Yamashita, and the incidence of 2 stems was 3.48%. We have modified the data of B⁶ and A⁶, and the classification of V⁶ is not affected.

Changes in the text: see Page8, line200--207.

#6 line 207-208

You have already mentioned the definition of variation." I guess it is very significant to show the branching pattern of "A6b originating from A9+10/A10 alone" and "A6c originating from A9+10", but can it be considered a variation?

Reply F #6: Thank you for your questions. As for the definition of variation, I think it is that the anatomical structure is different from that of most normal people, and the probability of occurrence is relatively low, but it is relatively important in our clinical work. Just as A^{6b} or A^{6c} originating from A⁹⁺¹⁰ may not make much difference in a dorsal segmentectomy, it can lead to inadequate intersegmental-plane or safety margin if it is incorrectly interrupted in a subsegmentectomy. For example, in a basal segment excision, a faulty A^{6b} or A^{6c} originating in A⁹⁺¹⁰/A¹⁰ can result in a retained superior segment dysfunction; In S⁶/S^{6b} combined with S^{8a} or combined with S^{8a}+S^{9a}, if the leak originates from A^{6b} or A^{6c} of A⁹⁺¹⁰/A¹⁰, it will result in reduced intersegmental-plane and insufficient safety margin. We believe that the distinction should still be made, especially during subsegmentectomy.

Changes in the text: None.

#7 line 209

"...Figure 2c).The segments and sub-segments of V6..." Wouldn't you be better off with a line break in this part or the part about the pulmonary veins?

Reply F #7: Thank you for your questions. For the sake of the unity of the whole text, we have decided not to add line breaks.

Changes in the text: None.

#8 line 217

What does "co-dry" mean?

Reply F #8: Thank you for your questions. To avoid confusion for readers, we have changed "V⁶ and V⁸⁺⁹ co-dry" to "co-draining of V⁶ and V⁸⁺⁹".

Changes in the text: see Page4, line80; Page9, line239.

Figure:

#9 Figure 1

This image shows two bronchi in B6. However, it is easier to understand the branching pattern if the image is shown with just the bronchi without the blood vessels superimposed. Perhaps it can be shown in one image instead of two.

Reply F #9: Thank you for your questions. We feel that this display image content is richer, more hierarchical sense.

Changes in the text: None.