Author’s response to reviews

Title: Solid component tumor doubling time is a prognostic factor in non-small cell lung cancer patients

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To the Editor-in-Chief, Journal of Cardiothoracic Surgery

Thank you for giving us the opportunity to submit a revised version of our manuscript entitled, “Solid component tumor doubling time is a prognostic factor in non-small cell lung cancer patients”. We have prepared response to reviewer’s comments and suggestions providing detailed answers and explanations.

Your consideration of our work is greatly appreciated.

Dear Reviewer #1,

Thank you very much for kind suggestions and comments and for giving us the opportunity to submit a revised manuscript. We have attempted to answer your questions in a detailed manner and revise our manuscript accordingly. Your consideration of our work is greatly appreciated.

1) They should describe radiological findings (mixed GGO or pure-solid tumors) in Table 1 and Table 2.
Reply: Thank you for pointing it out. It is important findings. We added the number of mixed GGO and pure-solid tumors in Table 1 and Table 2. As indicated, the rate of patients with pure solid tumors were significantly higher in TDT <400 group than in ≥400 group.

2) Once again it is important to describe radiological features. Moreover, authors should mention the reason why solid component TDTs influenced only prognoses in Stage IB patients.

Reply: Thank you very much. We added the number of mixed GGO and pure-solid tumors in each Table and compared them. There were no significant difference in patients with solid TDT <400 and ≥400 by radiological findings as Table 2.

We could not indicate clearly, we considered that factors other than TDT such as malignancy of tumor, immune status or vascular invasion could influence to the prognosis in Stage IA patients. Anyway, the number of patients with Stage I was slightly little, and further accumulation of cases is necessary. It is the subject of further study.

3) It would be reasonable to show whether the prognostic impact of solid component TDTs can apply to both mixed GGO tumors and pure-solid tumors.

Reply: Thank you for pointing it out. We indicate the Kaplan Meier curve (OS and RFS) in patients with pure-solid tumors and with mixed GGO in supplemental figure 1. As indicated, the patients with solid component TDT<400 were significantly poor OS and RFS in each group.

4) To prove that solid component TDTs really reflect prognoses rather than all component TDTs do, it would be preferable to include whole component TDTs into univariate and multivariate analyses (Table 3).

Reply: Thank you for pointing it out. As you pointing out, we could not conclude that solid component TDT is a stronger factor than whole component TDT only in Figure 5. As you say, it should perform the univariate and multivariate analyses about whole component TDT, however, whole component TDT and solid component TDT had statistically strong correlation, and we have not done these analyses.

5) Table 1 and Table 2: authors had better add percentage to numbers of patients. It will make tables easier to understand.

Reply: Thank you for pointing it out. We added the percentage in Table 1 and 2.

6) Page 4, line 8 (Methods): I do not think Figure 1 show the flow chart of patient selection. It would be wrong.
Reply: Thank you for pointing it out. It is our mistake. We change the sentence as below.

Before: Figure 1 shows the flow chart of patient selection and exclusion.

After: We indicate the patient selection and exclusion.

7) Page 4, line 16 (Methods): CT findings and how to calculate TDTs are shown in Figure 1. It should be "Figure 1" instead of "Figure 2".

Reply: Thank you for pointing it out. We corrected “Figure 2” to “Figure 1”

8) Page 8, line 8 (Results): It should be Table 2 instead of Table 3.

Reply: Thank you for pointing it out. We corrected “Table 3” to “Table2”.

9) Page 10, line 5 (Results): Table 4 is not shown in this paper.

Reply: Thank you for pointing it out. This is our mistake. We changed “Table 4” to “Table 3”.

Dear Reviewer #2

Thank you very much for kind suggestions and comments and for giving us the opportunity to submit a revised manuscript. We have attempted to answer your questions in a detailed manner and revise our manuscript accordingly. Your consideration of our work is greatly appreciated.

The findings are quite interesting although the paper in some parts results confusing. A lot of analyses and subanalyses have been done: in my opinion this big amount of data leads to confusion in the readers with the risk to lost the primary message. In fact, being the number of patients relatively low it is unuseful to do subanalyses on a small number of pts. I recommend to remove these results.

Reply: Thank you for pointing it out. As you say, the number of patients, particularly in Stage I, was slightly little. We consider this is one of the problems of this study and these results could lead to confusion. However, we would like to indicate the possibility that TDT could influence to the prognosis as the solid component grows larger at pStage I patients. We refer about this limitation in main text as further accumulation of patients is necessary, so we hope to leave it without deleting these analyses.
In addition to the retrospective fashion, there is another important limitation in this study: the radiological evaluation has been performed by two thoracic surgeons. Despite the assumption these surgeons are expert in radiology field for lung cancer it could be advisable that the radiological measures would be done by expert radiologists, in fact the simple diameter evaluation sometimes is not accurate to measure the tumor and its doubling time. This limitation should be underlined and addressed in the paper.

Reply: Thank you for pointing it out. As you pointing out, it could be important limitation and radiologists could have been to measure the doubling time. We added the sentences as below in page 13.

And then, the radiological evaluations have been performed by two thoracic surgeons. Although it performed under the guidance of radiologist, there might be a slight measurement error.

Dear Reviewer #3

Thank you very much for kind suggestions and comments and for giving us the opportunity to submit a revised manuscript. We have attempted to answer your questions in a detailed manner and revise our manuscript accordingly. Your consideration of our work is greatly appreciated.

1) The line numbers seem to be two overlapping numbers. Please chose one

2) Tables overlap the page lines, especially table 1 and table 2; please adjust them

Reply: Thank you for pointing it out. We changed main text and Tables as you indicated.