Author’s response to reviews

Title: Thin-section computed tomography-determined usual interstitial pneumonia pattern affects the decision-making process for resection in newly diagnosed lung cancer patients: a retrospective study

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Author’s response to reviews:

Our revisions in line with the reviewer's suggestions are as follows:

To Reviewer #1.

We really appreciate your whole comments for our manuscript.

As Reviewer #1 gave us the kind comments, our recent study assessing the impact of CPFE in patients with resected lung cancer had been published by the Annals of Thoracic Surgery 2016 (Reference No. 14: Ann Thorac Surg 102:440-447 2016). The incidence of postoperative complications including acute lung injury was significantly higher in the CPFE group. Survival curves indicated that a finding of CPFE was associated with worse overall survival for patients with any stage disease.
As we described in the introduction section in our original and revised manuscript, we noticed that less than 30% of patients with fibrosis had TSCT-determined usual interstitial pneumonia (UIP) pattern among resected lung cancer patients with fibrosis. Recent studies suggested that the finding of UIP pattern, representative for idiopathic pulmonary fibrosis (IPF), might be associated with acute exacerbation of interstitial lung diseases in patients with resected lung cancers (Reference No. 8: J Thorac Cardiovasc Surg 147:1604-1611. e1603 2013). Therefore, we hypothesized that TSCT-determined UIP pattern might affect the decision-making process for resection in newly diagnosed lung cancer patients, accompanied by our clinical experiences.

We would like to respond to the reviewer #1’s comments point by point as below.

**Major essential revisions.**

#5. The Reviewer #1 suggested the importance of the data about the relation between TSCT-determine fibrosis and postoperative complications among the patients with resected lung cancers. We totally agree with the comment. Fortunately, we recently reported this critical issue in Annals of Thoracic Surgery 2016 (Reference No. 14: Ann Thorac Surg 102:440-447 2016). To make it clear, we added the related sentences about the relation between the UIP pattern and acute lung injury among lung fibrosis patients with resected lung cancers in the Introduction section as follows:

Page 5 line 12 to 17:

TSCT-determined usual interstitial pneumonia (UIP) pattern is a characteristic finding of idiopathic pulmonary fibrosis (IPF) which has a death rate worse than that of many cancers [12, 13]. In patients with resected lung cancer, acute exacerbation of interstitial lung diseases might be associated with the finding of TSCT-determined UIP pattern [9].

#2. The Reviewer #1 kindly pointed out the insufficient explanation about variables for multivariable logistic regression analysis. We selected age, histology, severity of airflow obstruction, clinical lung cancer stage, severity of fibrosis as the variables, based on our previous study (Reference No. 6: BMC Pulmonary Medicine 14:14 2014). We described the comment in the discussion session in our present manuscript and also in Reference No. 6. We added the related sentences in Patients and Methods section as bellow:

Page 9 line 15 to 16:

including age, histology, severity of airflow obstruction, clinical stage, and severity of fibrosis [6].

#1. The Reviewer #1 kindly pointed out the absence of DLCO measurement for the surgical candidates. We totally agree with the comments. DLCO measurement was not performed in more than 40% of surgical candidates missing thoracic surgery. Spirometry screening assessment was routinely performed when patients admitted to hospital for bronchoscopy. Because DLCO is more complicated spirometry assessment than FEV1/FVC, spirometry screening assessment did not involve DLCO measurement. DLCO measurement is
recommended for screening in the patients undergoing thoracic surgery, according to the ERS and the ESTS clinical guideline. Multidisciplinary team members involving pulmonologists, thoracic surgeons, and radiologists, comprehensively evaluate whether the surgical candidates could receive resection of lung cancer. Some patients in the non-surgery group were those who finally did not receive surgery after DLCO assessment. DLCO might be closely associated with the existence and extent of chest CT-detected emphysema and fibrosis. Coexistence of TSCT-determined emphysema and fibrosis might affect the decision-making process for DLCO measurement with regards to postoperative residual lung function. As a consequence, when the teams decided not to propose surgery for the surgical candidates, DLCO measurement might not be proposed. In the study population, there was no information supporting the explanation that the patients who did not receive surgery and DLCO measurement might be more hyoxemic.

We have already described our interpretation about the absence of DLCO measurement in the Discussion Section in the original manuscript. We highlighted the sentences as red in the revised manuscript as below:

Page 16 line 15 to page 17 line 5,

Recent studies suggest that DLCO might be closely associated with the existence and extent of chest CT-detected emphysema and fibrosis [29, 30]. CPFE often involves upper lobe emphysema and lower lobe fibrosis [24]. The finding of TSCT-determined UIP pattern might affect survival in patients with CPFE [31]. DLCO measurement was performed for all 5 fibrosis patients, whereas more than 20% of CPFE patients did not have DLCO measurement (8/41 cases). Coexistence of TSCT-determined emphysema and fibrosis might affect the decision-making process for DLCO measurement with regards to postoperative residual lung function [32].

#3. The Reviewer #1 kindly commented the possible explanation for the absence of DLCO measurement. We really appreciate it. Sato, et al. suggested that %DLCO, not UIP pattern, did not have a significant and independent association with acute exacerbation incidence, which was congruent with the results reported by Kushibe and colleagues and Shintani and colleagues (Reference No. 8: J Thorac Cardiovasc Surg 147:1604-1611.e1603 2013). There might not be any guideline to recommend DLCO measurement for other therapeutic options such as chemotherapy, radiation, and palliative care. Taken together with the findings as above, we added the related sentence about the possible explanation for the absence of DLCO measurement as below:

Page 17 line 5 to 9:

The previous study suggested that %DLCO, not TSCT-determined UIP pattern, did not have a significant and independent association with acute exacerbation incidence of interstitial lung diseases in patients with resected lung cancers [9]. Thus, another possibility might be due to insufficient evidence to show the importance of DLCO measurement for lung cancer treatment.

#4. The Reviewer #1 kindly pointed out the insufficient explanation about our study including title and table 4 title, etc. We appreciate the kind comments. Taken together with our previous study (Reference No. 6: BMC Pulm Med 14:14, 2014), we believe that our data clearly showed
that the UIP pattern on TSCT evaluation was one of independent factors associated with the decision to perform thoracic surgery. We notice that retrospective analysis might have several limitations to determine hypothesis. Nevertheless, this study might make the readers to pay attention to this real world problem in clinical setting. We revised the title of Table 4 and added the related sentences as follows:

The revised title of Table 4; “Univariate and multivariate analysis of independent factors in decision-making process for proposing thoracic surgery with cure intent”

Page 18 line 6 to 7;

Although retrospective analysis might have several limitations to determine the hypothesis,…..

To Reviewer #2.

We really appreciate your comments for our manuscript.

In this study, multidisciplinary team members involving pulmonologists, thoracic surgeon, and radiologists, comprehensively evaluated whether the surgical candidates could receive resection of lung cancer. Indeed, it would be hard to identify honeycomb. As we described in Patients and Methods section, after the initial interpretation by at least two radiologists, the evaluation of fibrosis and honeycombing was performed by a chest radiologist (SI) who had 20 years of experiences in reading thoracic CTs. Based on the determination of fibrosis, we evaluated the impact of fibrosis severity on the decision-making process for resection in newly diagnosed lung cancer patients.