

Peer Review File

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Reviewer A

The authors showed that the pathological subtype size defined by the authors can be a prognostic factor for the prognosis after lobectomy in pStage IA-ADC, and pointed out that it is more important than the current subtype proportion. It can be said that the point is a very novel idea. Although it is doubtful whether the size evaluation derived from the maximum diameter of the tumor obtained from the pathological maximum section can represent the overall tumor burden, the result that subtype size can statistically be a predictor of postoperative prognosis is a message with clinical impact toward the improvement of future staging indices in surgical resection cases, and I believe that publication value is high.

I would like the following corrections:

#Line 42, and 184: “subtpe” will be “subtype”.

Reply:

Thank you. I made a mistake and we made a corrections

Table 2. Line Histologic subtype size, Papillary 0, MP 0, and Solid 0, will be typographical errors.

Reply: We demonstrated median size for each subtype but papillary, micropapillary and solid subtypes were rare in stage IA adenocarcinoma so their median size were zero

Please include any negative data left blank in Tables 3 and 4, multivariate column.

Reply: We used the multivariate analysis with forward selection so negative data was not indicated in the analysis sheet.

Reviewer B

This study analyzed prognostic significance of the histological subtype size using multiplying the tumor’s maximum diameter by the proportion of each histologic subtype. The disease-free interval (DFI) was significantly different following each histologic subtype size, and the results were confirmed with multivariate analysis.

Major concerns of this reviewer are as follows.

1. Pathologists believe that histological characteristics affect the aggressiveness of the tumors. In fact, predominant subtypes of adenocarcinoma were associated with patients’ outcome in multiple studies. Therefore, Histological subtyping is used for prediction of therapeutic response and prognosis. However, this study focused on biological behavior of individual subtypes as a group. How do the authors use this finding in clinical practice? Particularly, it has been shown that predominant adenocarcinoma subtypes

are associated with prognosis. What is the significance of this study in addition to known knowledge?

Reply: From IASLC, there were two important prognostic factors in early stage lung non mucinous adenocarcinoma. (Predominant subtype and invasive size).

Our study demonstrate the each subtype size has prognostic role and it may indicate invasive size. So prognosis could be predicted using our simple calculation formula. (Page 10, Line 215, Page 11, Line 243-244)

2. The adenocarcinoma grading has been introduced by the IASLC pathology committee. The adenocarcinoma grades were shown to be more closely associated with the prognosis than that of predominant subtypes. Why would the authors compare the grade with the authors' results?

Reply: Our previous study (reference 4) was the validation study of grading system. However, there was no significance in multivariate analysis in this our study and we added some data as your comments (Page 7, Line 138-140, Table 2 and 3)