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Response to comment on: "Correlation of Tumor Spread through Air Spaces and Clinicopathological Characteristics in Surgically Resected Lung Adenocarcinomas."

We appreciate the interest and comments for our article, titled "Correlation of Tumor Spread through Air Spaces and Clinicopathological Characteristics in Surgically Resected Lung Adenocarcinomas [1]".

First, we thank the authors for the comment regarding to the correlation of histopathological patterns and tumor spread through air spaces (STAS). In our study, STAS was defined as tumor cells (arranged as single cells, micropapillary clusters, or solid nests) observed within the alveolar spaces in the surrounding lung parenchyma beyond the edge of the main tumor and was reviewed microscopically by a pathologist (M-S Hsieh). The pathological staging was based on the AJCC 8th edition staging [2], and were collected from the patients' medical chart. One patient with previously documented minimally invasive adenocarcinoma in medical chart was noted to be positive STAS in the microscopically re-evaluation process. This patient should be re-classified as T1a rather than T1mi according to the 2015 World Health Organization criteria [3]. We apologized for the mistake and revised this part in the corrigendum.

We performed the statistical analysis according to the authors' suggestion, that the micropapillary and solid patterns as predominant subtypes should be analyzed as a variable in multivariate analysis rather than lepidic pattern. In the multivariate analysis, positive STAS was significantly related to predominant micropapillary/solid subtype patterns, moderate/poor differentiation, lymphovascular invasion, and higher T and N stages. There have been several studies showed the correlation of invasive histopathological patterns and positive STAS [4,5], which is consistent with our finding.

We are grateful for the comment on the artificial effects of STAS evaluation. We also mentioned about the limitation in our manuscript [1]. It is necessary to uniform the pathological specimen processing protocol in handling to minimize the possibility of artifact-related STAS. Further studies on the artefact that lead to false-positive STAS expression are necessary to reduce the false positive rate. Also, more investigations regarding to the definition of STAS may reduce the confounding bias.

Although STAS has been showed to be a significant prognostic factor in non-small cell lung cancer patients [1,4,5], more studies are necessary to made STAS as a staging profile in future staging system.

Conflict of interest

The authors declare no conflicts of interest.

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