Letter to the Editor

What is spread through air space?

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Provenance: This is an invited article commissioned by Section Editor Dr. Gang Shen, MMSC (The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China).

Response to: Warth A. Spread through air spaces (STAS): prognostic impact of a semi-quantitative assessment. J Thorac Dis 2017;9:1792-5.
Morales-Oyarvide V, Mino-Kenudson M. Taking the measure of lung adenocarcinoma: towards a quantitative approach to tumor spread through air spaces (STAS). J Thorac Dis 2017;9:2756-61.

Submitted Aug 15, 2017. Accepted for publication Aug 24, 2017.
doi: 10.21037/jtd.2017.08.159
View this article at: http://dx.doi.org/10.21037/jtd.2017.08.159

Recently, aerogenous tumor spread was recognized as a prognostic factor in the pathologic diagnosis of lung adenocarcinoma. Onozato *et al.* (1) showed that a tumor island, which is defined as an isolated, large collection of tumor cells within alveolar spaces that lack a well-demarcated micropapillary configuration, increased the risk of recurrence in patients with stage I lung adenocarcinoma. Interestingly, the connection of a tumor island to the main tumor was demonstrated by three-dimensional reconstruction analysis. Kadota *et al.* (2) reported that tumor spread through air spaces (STAS), defined as the presence of tumor cells that goes beyond the edge of the main tumor to within at least the first alveolar layer in the lung parenchyma, was a significant risk factor for recurrence of small (≤2 cm) lung adenocarcinoma in patients who underwent limited resection. The 2015 World Health Organization classification (3) introduced STAS as a new route of invasion and included it in the exclusion criteria for minimally invasive adenocarcinoma. A study by Warth *et al.* (4) defined STAS as detachment of small solid cell nests (at least 5 tumor cells) away from the main tumor mass and classified it according to the distance from the main tumor mass as limited type (<3 alveolar layers) or extensive type (>3 alveolar layers). That study showed that the presence of STAS, regardless of extent, significantly reduced recurrence-free survival and overall survival of patients with resected adenocarcinoma of any stage.

More detailed studies have investigated factors besides the presence or absence of STAS. First, the meaning of small amount of STAS was examined. Uruga *et al.* (5) semiquantitatively made a classification of no STAS based on the definition by Kadota *et al.* (2); low STAS (1–4 single cells or clusters of STAS); and high STAS (5 single cells or clusters of STAS) with a 20× objective and a 10× ocular lens. We showed that semiquantitative assessment was a useful prognostic factor in patients with small (≤2 cm) lung adenocarcinoma. Although several studies found presence of STAS to be a worse prognostic factor, its influence in staging was unknown. Dai *et al.* (6) showed that patients with stage I adenocarcinoma <2–3 cm and the presence of STAS, which was based on the definition by Kadota *et al.* (2), had prognosis similar to that of patients with stage IB adenocarcinoma; therefore, STAS may possibly change the pathologic stage of a tumor.

The concept of STAS has also been applied to squamous cell carcinoma of the lung. Lu *et al.* (7) showed that STAS was present in one-third of patients with resected squamous cell carcinoma of the lung and that the cumulative recurrence rate was significantly higher in patients with STAS than in those without STAS; however, there was no statistically significant difference in overall survival. Kadota *et al.* (8) reported that STAS was an independent prognostic factor for worse recurrence-free survival according to multivariate analysis in a Japanese cohort.

However, the bottom line is that the concept of STAS remains a subject of debate. Thunnissen *et al.* (9) pointed

out that during lung resection and specimen preparation, tumor cells may be displaced by the knife along the plane of sectioning; this concept was termed spreading through a knife surface (STAKS). Loose tissue fragments can be not only tumor cells, but also airways, blood vessels, alveolar ducts, and alveolar sacs. Blaauwgeers *et al.* (10) performed a prospective, multicenter study of 44 lung cancer resection specimens to confirm the concept of STAKS. First, the specimens were cut with a clean long knife, followed by a second incision parallel to the plane of the first cut without cleaning the knife. Next, they divided the two pieces into two sections each to make four formalin-fixed paraffin-embedded tissue blocks. The total number of fields with tumor clusters was 244 in all blocks and 16, 62, 82, and 84 in the blocks 1 to 4, respectively, for each of the blocks. They concluded that 93% of the loose tissue fragments could be explained by mechanical forces associated with tissue handling.

What is STAS? At present, we do not have a precise answer to this question and the concept of STAS is still being debated. Some part of STAS could be explained by the presence of artifacts during specimen preparation, but several studies have shown that STAS is associated with worse recurrence-free survival. Furthermore, multivariate analysis in several studies has shown that STAS is an independent prognostic factor of adenocarcinoma subtypes, including those with micropapillary pattern. Further studies are needed to answer the question, "What is STAS?"

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Uruga H, Fujii T, Kishi K. What is spread through air space? J Thorac Dis 2017;9(10):E943-E944. doi: 10.21037/jtd.2017.08.159

