Editorial Commentary

Spread through air spaces in non-small cell lung cancer

Yuka Kozuma[1], Gouji Toyokawa[1], Yuichi Yamada[2], Fumihiro Shoji[1], Koji Yamazaki[1], Yoshinao Oda[2], Sadanori Takeo[1]

[1]Department of Thoracic Surgery, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Chuo-ku, Fukuoka, Japan; [2]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan

Correspondence to: Gouji Toyokawa, MD, PhD. Department of Thoracic Surgery, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563, Japan. Email: gouji104kawa@gmail.com.

Provenance: This is an invited article commissioned by the Academic Editor Shuang-Jiang Li (Department of Thoracic Surgery and West China Medical Center, West China Hospital, Sichuan University, Chengdu, China).

Comment on: Chen D, Mao Y, Wen J, *et al.* Tumor Spread Through Air Spaces in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Ann Thorac Surg 2019;108:945-54.

Submitted Jun 28, 2019. Accepted for publication Aug 15, 2019.
doi: 10.21037/jtd.2019.08.97
View this article at: http://dx.doi.org/10.21037/jtd.2019.08.97

In 2015, a newly defined cancer growth pattern was identified. Classified as spread through air spaces (STAS) by The World Health Organization (WHO), STAS is best understood as a new form of cancer invasion.

STAS is defined as the presence of tumor cells including micropapillary clusters, solid nests or single cells apart from the primary lesion that spread through the air spaces in the surrounding lung parenchyma (1). In April 2019, Chen *et al.* published the report entitled "Tumor Spread Through Air Spaces in Non-Small Cell Lung Cancer: a systematic review and meta-analysis" in *Annals of Thoracic Surgery* (2). While an increasing number of studies have tried to reveal the clinical significance of STAS, it remains a controversial topic of study. Therefore, this meta-analysis may serve as important research to clarify the significance of STAS. In this meta-analysis, the investigators systematically reviewed the studies on the correlation between STAS and prognosis in patients with lung cancer and concluded STAS could be a prognostic predictor for patients with resected non-small cell lung cancer (NSCLC). The authors evaluated 14 published studies including 3,754 patients across various histological types and showed that STAS was associated with worse recurrence-free survival (RFS) [hazard ratio (HR) =1.975, 95% confidence interval (CI): 1.691–2.307, P<0.001] and overall survival (HR =1.75, 95% CI: 1.375–2.227, P<0.001). Subgroup analysis of histological subtypes showed that STAS was significantly correlated with worse RFS in adenocarcinoma (HR =2.288, 95% CI: 1.843–2.840, I^2=7.80%), squamous cell carcinoma (HR =1.622, 95% CI: 1.279–2.056, I^2=0%) and pleomorphic carcinoma (HR =4.76, 95% CI: 1.168–19.398). The results appear to be clinically meaningful and the current meta-analysis is associated with several concerns.

First of all, in the studies conducted so far, the definition and diagnosis of STAS are not consistent. As shown in this meta-analysis, the frequency of STAS considerably varies among the reports, which means the inconsistent evaluation of STAS. Moreover, further classifications of STAS are slightly different depending on the study, even though the precise definition of STAS has been proposed by WHO. The most common method to identify STAS is based on morphologic features, including single cell, small clusters, and tumor cell nests, which is how WHO defines it.

Other classifications focus on the quantity and the distance of STAS from the main tumor, which are not described in the WHO criteria. Several studies defined STAS as the presence of tumor cells whose distance from the edge of primary lesion as in the first alveolar spaces, and others defined as at least a few alveolar spaces (3-6). Warth *et al.* divided the extent of STAS into two groups according to the distance from the main tumor (7). They defined 'limited STAS' as a solid cell nest no more than three alveoli away from the main tumor mass. 'Extensive STAS' was defined as a tumor cell nest more than three alveoli away from the tumor edge. Similar categorization of STAS was adopted in a study by Lu and colleagues (5).

Another classification of STAS was focused on its quantity. Uruga *et al.* performed a quantitative assessment of STAS, dividing the grades of STAS into three levels: no STAS, low STAS (1–4 cells or clusters), and high STAS (>4 cells or clusters) (6). In this study, the grades of STAS were reported to be associated with the clinical significance of STAS, based on clinicopathological features and prognosis. Although further validation of these classifications is required, these results indicate that the extent and quantity of STAS might reflect how the tumor progresses and invades.

Considering the progression style of STAS, it seems that there are many trans-airway metastasis and stump recurrences; however, most of the reported studies have not adequately discussed whether the presence of STAS influenced the recurrent pattern. Furthermore, as described in this meta-analysis study, STAS is associated with poor prognosis in patients who performed limited resection, although it remains controversial whether as is in patients who undergo lobectomy. Our previous report showed that STAS also negatively impacted on the RFS in patients with lobectomy (8). Warth *et al.* found that STAS is a novel prognosticator in 569 resected pulmonary adenocarcinomas patients, of whom 83% underwent lobectomy (7). In a recent report by Eguchi *et al.*, the presence of STAS in T1 lung adenocarcinoma is associated with higher recurrence and cancer-specific death in patients with sublobar resection than in those who underwent lobectomy (9). Furthermore, the most common recurrence pattern in patients with STAS who performed sublobar resection was locoregional recurrence, regardless of margin-to-tumor ratio. Shiono *et al.* reported that STAS-positive patients with sublobar resection developed pulmonary metastases more frequently than patients with STAS-negative treated with lobectomy (10). Taken together, these findings suggest that STAS might be associated with locoregional and trans-airway metastasis. Therefore, limited resection should be avoided for patients with STAS. However, predicting the STAS status before surgery was difficult. Our previous study evaluating the association of STAS with computed tomography (CT) findings showed that the presence of notch and the absence of ground grass opacity were independently associated with STAS, and it might be helpful to identify the presence of STAS using CT images before surgery (11). Furthermore, it is unclear whether the prognostic significance of STAS varies by tumor size or stage. Dai *et al.* reported the prognostic significance of STAS only in patients with small size tumors (12). By contrast, we demonstrated that STAS was an independent prognostic factor of RFS in completely resected adenocarcinomas with lymph node metastasis (13). The significance of STAS in therapeutic strategies, including surgical procedure and adjuvant therapy, needs to be examined in future investigations.

The clinical significance of STAS has been reported in many studies, but a sufficient biological explanation of STAS has not been adequately identified. STAS was shown to be frequently found in tumors with *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) mutations, *epidermal growth factor receptor* (*EGFR*) wild-type and *anaplastic lymphoma kinase* (*ALK*) fusions (3,14,15). Several attempts have been made to examine the biological significance of STAS in terms of cell adhesion, epithelial-mesenchymal transition (EMT), and tumor stromal cells. Liu *et al.* reported that metastasis-associated protein 1 (MTA1), which is involved in several signal transduction pathways and associated with invasive and metastatic phenotypes, was more frequently expressed in STAS-positive patients (16). MTA1 also represses E-cadherin and induces EMT, possibly resulting in the tumor invasion and metastasis (17). Recently, Hara *et al.* reported SLX, a cell adhesion protein in the selectin family, had no relation with the presence of STAS (18). Qiu *et al.* evaluated the relationship between STAS and stromal cells, and the presence of STAS was reported to be associated with a high frequency of α-SMA-positive cancer associated fibroblasts and CD204-positive tumor associated macrophages (19).

However, these results are not sufficient to explain the *in vivo* effect of STAS and therefore, some reports suggest that STAS might be no more than "loose tumor fragments" or artifacts caused by spreading through a knife surface (STAKS) (20). Before the concept of STAS was defined by WHO in 2015, Onozato *et al.* used a three-dimensional reconstruction model to demonstrate that tumor islands isolated within alveolar spaces, whose morphological feature is similar to STAS, were connected with the primary tumor at different levels. These features could not be recognized by routine observation of histology slides (21). Blaauwgeers *et al.* explained STAS as an artifact derived from the handling procedure. In a prospective multicenter study, they showed that the number of free tumor cells within air spaces is increased cut-by-cut and concluded that 93% of the STAS could be explained by mechanical forces associated with tissue handling (22). However, if STAS is just an artifact, it is difficult to explain the clinical significance as shown in this meta-analysis. Further studies are warranted to optimally distinguish between STAS and STAKS and to

clarify the biological significance of STAS.

STAS is a new concept that is still controversial and it is crucial to establish an accurate definition. As mentioned above, the criteria of STAS, including tumor cell numbers and the distance from the tumor edge, is not clearly described in the WHO definition. Therefore, it is necessary to globally establish the evaluation criteria of STAS.

In conclusion, this meta-analysis showed that STAS could be a prognosticator in NSCLC patients, although it remains unclear whether STAS is induced by an *in vivo* effect or just artifacts of cutting through a tumor with a knife. Future prospective studies are necessary to elucidate the true significance of STAS in regards to surgical handling, pathological preparation for slides, and coming to a consensus on how STAS is evaluated.

Acknowledgments

We would like to thank Ms. Rachel Sharpton for her editing work on the manuscript.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
2. Chen D, Mao Y, Wen J, et al. Tumor Spread Through Air Spaces in Non-Small Cell Lung Cancer: a systematic review and meta-analysis. Ann Thorac Surg 2019;108:945-54.
3. Kadota K, Nitadori J, Sima CS, et al. Tumor Spread through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences after Limited Resection for Small Stage I Lung Adenocarcinomas. J Thorac Oncol 2015;10:806-14.
4. Dai C, Xie H, Su H, et al. Tumor spread through air spaces (STAS): a call for more evidence. J Thorac Dis 2017;9:E951-3.
5. Lu S, Tan KS, Kadota K, et al. Spread through Air Spaces (STAS) Is an Independent Predictor of Recurrence and Lung Cancer-Specific Death in Squamous Cell Carcinoma. J Thorac Oncol 2017;12:223-34.
6. Uruga H, Fujii T, Fujimori S, et al. Semiquantitative Assessment of Tumor Spread through Air Spaces (STAS) in Early-Stage Lung Adenocarcinomas. J Thorac Oncol 2017;12:1046-51.
7. Warth A, Muley T, Kossakowski CA, et al. Prognostic Impact of Intra-alveolar Tumor Spread in Pulmonary Adenocarcinoma. Am J Surg Pathol 2015;39:793-801.
8. Toyokawa G, Yamada Y, Tagawa T, et al. Significance of Spread Through Air Spaces in Resected Pathological Stage I Lung Adenocarcinoma. Ann Thorac Surg 2018;105:1655-63.
9. Eguchi T, Kameda K, Lu S, et al. Lobectomy Is Associated with Better Outcomes than Sublobar Resection in Spread through Air Spaces (STAS)-Positive T1 Lung Adenocarcinoma: A Propensity Score-Matched Analysis. J Thorac Oncol 2019;14:87-98.
10. Shiono S, Endo M, Suzuki K, et al. Spread Through Air Spaces is a Prognostic Factor in Sublobar Resection of Non-Small Cell Lung Cancer. Ann Thorac Surg 2018;106:354-60.
11. Toyokawa G, Yamada Y, Tagawa T, et al. Computed tomography features of resected lung adenocarcinomas with spread through air spaces. J Thorac Cardiovasc Surg 2018;156:1670-6.e4.
12. Dai C, Xie H, Su H, et al. Tumor Spread through Air Spaces Affects the Recurrence and Overall Survival in Patients with Lung Adenocarcinoma >2 to 3 cm. J Thorac Oncol 2017;12:1052-60.
13. Toyokawa G, Yamada Y, Tagawa T, et al. Significance of Spread Through Air Spaces in Resected Lung Adenocarcinomas With Lymph Node Metastasis. Clin Lung Cancer 2018;19:395-400.e1.
14. Onozato ML, Kovach AE, Yeap BY, et al. Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. Am J Surg Pathol 2013;37:287-94.
15. Lee JS, Kim EK, Kim M, et al. Genetic and clinicopathologic characteristics of lung adenocarcinoma with tumor spread through air spaces. Lung Cancer 2018;123:121-6.
16. Liu Y, Chen D, Qiu X, et al. Relationship between MTA1 and spread through air space and their joint influence on

prognosis of patients with stage I-III lung adenocarcinoma. Lung Cancer 2018;124:211-8.
17. Pakala SB, Singh K, Reddy SD, et al. TGF-beta1 signaling targets metastasis-associated protein 1, a new effector in epithelial cells. Oncogene 2011;30:2230-41.
18. Hara K, Mizuguchi S, Okada S, et al. Intensity of SLX predicts distance of tumor spread through alveolar spaces in stage I lung adenocarcinoma. Thorac Cancer 2019;10:832-8.
19. Qiu X, Chen D, Liu Y, et al. Relationship between stromal cells and tumor spread through air spaces in lung adenocarcinoma. Thorac Cancer 2019;10:256-67.
20. Blaauwgeers H, Russell PA, Jones KD, et al. Pulmonary loose tumor tissue fragments and spread through air spaces (STAS): Invasive pattern or artifact? A critical review. Lung Cancer 2018;123:107-11.
21. Onozato ML, Klepeis VE, Yagi Y, et al. A role of three-dimensional (3D)-reconstruction in the classification of lung adenocarcinoma. Anal Cell Pathol (Amst) 2012;35:79-84.
22. Blaauwgeers H, Flieder D, Warth A, et al. A Prospective Study of Loose Tissue Fragments in Non-Small Cell Lung Cancer Resection Specimens: An Alternative View to "Spread Through Air Spaces". Am J Surg Pathol 2017;41:1226-30.

Cite this article as: Kozuma Y, Toyokawa G, Yamada Y, Shoji F, Yamazaki K, Oda Y, Takeo S. Spread through air spaces in non-small cell lung cancer. J Thorac Dis 2019;11(Suppl 15):S1881-S1884. doi: 10.21037/jtd.2019.08.97

