

Tumor spread through air spaces (STAS): a call for more evidence

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We would like to thank Dr. Chen and his colleagues for their interest and positive comments concerning our work (1). The tumor spread through air spaces (STAS), which has been defined as tumor cells (single cells, micropapillary clusters, or solid nests) within air spaces in the surrounding lung parenchyma beyond the edges of the main tumor, was first introduced in the 2015 World Health Organization (WHO) classification for lung cancer and formally proposed as a new invasive pattern of adenocarcinoma (ADC) (2). After that, STAS attracted tremendous interest and has been studied more intensely (3).

The negative prognostic impact of STAS in patients with lung cancer has been thoroughly investigated. First, the initial study by Kadota and his colleagues found that STAS was closely associated with a higher risk of disease recurrence in lung ADCs (4). Soon after that, two retrospective studies from Western and Asian populations further extended the prognostic significance of STAS in patients with squamous cell carcinoma (SCC) (5,6). However, the morphological features of STAS were entirely different in ADCs and SCCs. The most common STAS pattern in ADCs was a micropapillary cluster (7), while all cases of SCC showed solid nest STAS (5,6). Second, the initial study also suggested that STAS is a significant risk factor for locoregional and distant recurrence in patients who underwent limited resection, but not in those who underwent lobectomy (4). Nevertheless, several recently published studies, including ours, have proved that the

presence of STAS is closely related to reduced recurrence-free survival (RFS) and overall survival (OS) even in patients who underwent lobectomy (7,8). The largest case series consisting of more than 1,000 early stage ADCs (≤ 2 cm) has also confirmed that patients without STAS had better survival outcomes than those with STAS independent of resection type (lobectomy or limited resection) (9). Of note, the 5-year cumulative incidence of local and regional recurrence (CIR) in patients with STAS was nearly five times higher than those without STAS in the limited resection group (5-CIR, STAS positive versus STAS negative, 31.1% versus 6.8%); CIR was less than double in the lobectomy group (5-CIR, STAS-positive versus STAS negative, 4.8% versus 2.8%), which might suggest that STAS not only represented the tumor's invasive capability, but also indicated potential residual tumor cells in surgical margins for patients who underwent limited resection. Third, single tumor cells observed within air spaces beyond the edges of the main tumor is enough for a STAS positive diagnosis. Thus, the current diagnostic criteria of STAS is deficient and needs further improvement. Several studies have aimed to associate STAS with prognostic significance by focusing on the quantity and the distance of STAS from the main tumor (10). Uruga and his colleagues proposed a semiquantitative approach to stratify the cases into no STAS, low STAS (1–4 single cells or clusters), and high STAS (≥ 5 single cells or clusters) (10). Survival analyses demonstrated that the RFS decreased significantly with the

increasing amount of STAS (median RFS: 154.2 months with no STAS, 147.6 months with low STAS, and 115.6 months with high STAS; $P < 0.001$). The association between the extent of STAS and patient prognosis is another concern. Our study failed to recognize a more negative influence of extensive STAS (>3 alveoli) on RFS and OS when compared with limited STAS (≤ 3 alveoli) (7). Similar results were also reported in other studies (5,11). These results indicated that the quantity of STAS might be a better prognostic risk factor than the extent of STAS.

All of these studies consistently showed that STAS should not be ignored and suggested that it be recorded in pathology reports, but additional evidence (except the prognostic value) is essential before STAS can be widely applied in clinical settings. First, the presence of STAS in published studies was diagnosed by retrospectively reviewing the haematoxylin and eosin-stained slides of resected tumor specimens. Recently, a prospective, multi-institutional study by Blaauwgeers and his colleagues argued that STAS could represent free-floating cell clusters during lung specimen handling, named as “*Spread Through A Knife Surface (STAKS)*” (12). More importantly, the results also indicated that the majority of STAS (93%) could be explained by dissemination along the prospecting knife blade. On the other hand, Lu and his colleagues reported three cases that sufficiently proved that STAS represented an invasive pattern rather than an artifact (13). For example, one male patient underwent wedge resection for a lung ADC in the right upper lobe. However, STAS could only be observed in the surgical margin. After a complete right upper lobectomy, the presence of STAS also could be identified in the remaining right upper lobe. These results suggest that a part of STAS was caused during the processing of specimen by the pathologist; thus, a standard protocol of lung specimen handling is needed to avoid STAKS. After successfully separating STAS from floaters, a perspective study should be performed to validate the prognostic impact of STAS. Second, some studies have found that patients with early stage lung cancer could be stratified by STAS (7,9). In our study, the survival outcomes of patients with ADC $>2-3$ cm/STAS-positive was similar to that of patients with stage IB ADC. However, we need more data to clarify whether patients with ADC $>2-3$ cm/STAS-positive would benefit from postoperative chemotherapy. Finally, the presence of STAS might suggest the presence of residual tumor cells in surgical margins for patients who underwent limited resection. Thus, detection of the STAS pattern in surgical margins on frozen sections is of

great concern. Only one study reported that the sensitivity, specificity, and accuracy of STAS pattern diagnosis in frozen sections were 71%, 92.4%, and 80%, respectively, but more studies are warranted to verify these results (14).

In conclusion, although the concept of STAS was proposed <3 years ago, its pathologic features and prognostic values have been clearly studied. However, more evidence would be extremely useful in order to confirm the potential significant impact of STAS for treatment decisions in clinical practice.

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Footnote

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

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