Editorial Commentary

What did the first meta-analysis of tumor spread through air spaces (STAS) bring to light?

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Tumor spread through air spaces (STAS) was recently identified as a new pattern of lung cancer invasion, in which floating tumor cells or clusters spread into adjacent air spaces beyond the edge of a lung tumor. Kadota *et al.* (1) reported that the presence of STAS was a significant risk factor for shorter recurrence-free survival (RFS) in patients with ≤2 cm lung adenocarcinoma treated by limited resection. STAS was noted to be a new route of invasion in the 2015 World Health Organization classification (2) and was defined as an exclusion criterion for minimally invasive adenocarcinoma. Uruga *et al.* (3) showed that semiquantitative assessment of STAS was useful for more detailed prognostic analysis. Dai *et al.* (4) suggested that the presence of STAS could potentially change the staging of lung cancer. In subsequent work, the concept of STAS was broadened from lung adenocarcinoma to include lung squamous cell carcinoma (5,6) and pleomorphic carcinoma (7).

However, some problems related to STAS remained. First and foremost was whether STAS was real or an artifact. Thunnissen *et al.* (8) pointed out that tumor cells could spread into alveolar spaces iatrogenically by the knife during pathological resection and named this phenomenon spread through a knife surface (STAKS). A second problem was the varying definitions of STAS. The original and most popular definition by Kadota *et al.* (1) was the presence of tumor single cells or cell clusters within air spaces in the lung parenchyma beyond the tumor edge, even if present in only the first alveolar layer. However, Warth *et al.* (9) defined STAS as tumor cell clusters containing at least 5 tumor cells in air spaces. A third problem was that all the studies were performed in a single center or hospital, and there was no interobserver study across different hospitals. These problems could cause bias in research on STAS.

To resolve some of these problems, Chen *et al.* (10) performed the first systematic review and meta-analysis of STAS. They systematically searched the literature on STAS, which contained prognostic analyses of hazard ratios (HRs) for RFS and overall survival (OS), and also evaluated the quality of the literature. They selected 14 of 132 articles for inclusion in the meta-analysis, and analyzed 2,897 non-small-cell lung carcinoma cases. First they analyzed RFS in association with clinicopathological parameters including STAS. The presence of STAS was associated with shorter RFS (HR: 1.975, 95% CI: 1.691–2.307, P<0.001). Heterogeneity was absent (Q=12.92, P=0.299, I^2=14.80%). In a subgroup analysis of tumor histology, the presence of STAS was significantly associated with shorter RFS in all three histologies of adenocarcinoma, squamous cell carcinoma, and pleomorphic carcinoma. For all clinicopathological parameters, including age, study area, and follow-up period, STAS was associated with shorter RFS, and the heterogeneity between studies was almost

absent to moderate. In addition, all included studies showed a similar trend in the pooled HR. Secondly, they analyzed OS. STAS was associated with shorter OS (HR: 1.75, 95% CI: 1.375–2.227, P<0.001), and the heterogeneity between studies was moderate (Q=17.06, P=0.048, I^2=47.20%). In a subgroup analysis of tumor histology, STAS was associated with significantly shorter OS in adenocarcinoma, but not in squamous cell carcinoma and pleomorphic carcinoma. STAS was not a significant prognostic factor in research conducted in the United States, and for a subgroup with a shorter follow-up period (<50.5 months). Heterogeneity was low for many factors, such as publication year, time of initial inclusion, number of patients, follow-up duration, and quality score.

This meta-analysis by Chen *et al*. (10) brought some interesting points to light. First, STAS was reproducibly found to be associated with significantly worse RFS and OS in the included studies. Reproducibility under slightly different definitions of STAS and with different pathologists in different institutions is important, especially in pathological studies. In addition, there were some differences in definitions of STAS. This reproducibility proven by the meta-analysis by Chen *et al*. (10), might increase the pathological importance of STAS. Second, the HR for RFS seemed to be higher in Asian countries than in the United States. In addition, the presence of STAS was identified as a significant negative prognostic factor for OS in Japan and China, an almost significant factor in Germany, but a non-significant factor in the United States. Some reasons for this were suggested. The difference in pathologists' ways of thinking between the United States and Asia might be a possible explanation for the result. However, Dr. Kadota performed studies on STAS in both the United States (1) and Japan (5). Another possible reason is that the presence of STAS is associated with lower EGFR mutations (9,11), and EGFR mutations in lung adenocarcinoma are more frequent in Asian patients than in Caucasian patients (12). We need more studies and discussion at this point. Finally, the HR for RFS seemed to be higher in adenocarcinoma than in squamous cell carcinoma. STAS was also found to be a significant negative prognostic factor for OS in adenocarcinoma, but not in squamous cell carcinoma. The reason for this is not known but differences in tumor progression might be a possible explanation. The alveolar filling type of lung squamous cell carcinomas, where tumor nests preserve the alveolar structure, had better RFS than the expanding type, where tumor nests destroy the alveolar structure (13). Alveolar space-filling type squamous cell carcinoma might appear as STAS in tangential section when it spreads like the roots of a tree or the limbs of an octopus. Some cases of alveolar space-filling type squamous cell carcinoma with STAS-like structure might have a better prognosis in lung squamous cell carcinoma compared with adenocarcinoma.

Two questions remain, however, following the study of Chen *et al*. (10). First, as the authors noted in the article, their meta-analysis could not address the question of whether STAS was real or an artifact. This point cannot be resolved by statistical methods. Second, although two investigators independently performed the literature search and evaluated the quality of the literature, the authors did not mention the concordance between the two investigators.

In conclusion, Chen *et al*. (10) performed the first meta-analysis of STAS. Previous studies on STAS were relatively small and conducted in single centers. As such, the results of this meta-analysis confirmed the importance of STAS. Further studies are awaited to resolve the remaining questions about STAS.

Acknowledgments

None

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.

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