Editorial

# Will spread through air spaces be a staging parameter in lung cancer?

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In the wake of the publication of the multidisciplinary lung adenocarcinoma classification [International Association for the Study of Lung Cancer, American Thoracic Society, European Respiratory Society (IASLC/ATS/ERS)] in 2011 (1), tumor morphology was recognized as a prognostic factor as important as other well-known clinicopathologic features including stage. Patients with lepidic-predominant adenocarcinoma have the most favorable prognosis followed by those with acinar or papillary adenocarcinoma. Those with solid or micropapillary adenocarcinoma have the worst prognosis (2,3).

More recently, multiple groups have shown that the presence of tumor cells in air spaces away from the tumor boundary is a prognostic factor. Onozato *et al.* (4) identified a tumor island (a large cluster of tumor cells present within alveolar spaces that lack a micropapillary structure) using 3D reconstruction and showed that tumor islands were connected to each other and the main tumor. Importantly, the presence of tumor islands was associated with an almost 2-fold increase in the risk of recurrence after resection of early stage lung adenocarcinomas (5). Kadota *et al.* (6) reported that tumor spread through air spaces (STAS)—the spread of single tumor cells or micropapillary/solid type tumor cell clusters within normal air spaces adjacent to the main tumor—was a significant risk factor for the recurrence of small lung adenocarcinomas (≤2 cm) in patients who have undergone limited resection. Subsequently, the 2015 World Health Organization (WHO) classification (7) introduced STAS as a new form of invasion and included it as an exclusion criterion for minimally invasive adenocarcinoma. Since then, a few groups looked at the prognostic significance of the extent of STAS. Warth *et al.* (8) classified SATS into limited and extensive types with the limited type defined as isolated small solid tumor cell nests (at least 5 tumor cells) <3 alveolae away from the main tumor and the extensive type defined as tumor cell nests >3 alveolae away from the main tumor. With their definitions, no difference was found in recurrence-free survival (RFS) and overall survival (OS) between limited and extensive types of STAS in patients with resected adenocarcinomas of any stage, although the presence of any STAS significantly reduced RFS and OS. Conversely, Uruga *et al.* (9) demonstrated the usefulness of semiquantitative assessment of STAS in predicting outcomes in patients with small lung adenocarcinoma (≤2 cm). In their study, using the definition by Kadota *et al.* (6), STAS was further classified into no STAS, low STAS (1–4 single cells or clusters of STAS), or high STAS (>5 single cells or clusters of STAS) with a 200× magnification.

Given that several studies have confirmed that STAS is associated with worse patient outcomes, STAS may be considered as a parameter of lung cancer staging, in particular for lung adenocarcinoma. To answer this question, Dai *et al.* (10) studied the influence of STAS on T

staging in a total of 383 patients with adenocarcinomas 3 cm or smaller [stage IA based on American Joint Committee on Cancer, 7th edition (11)] and 161 patients with stage IB adenocarcinomas. STAS was identified in 116 stage IA adenocarcinomas (30.3%), and was more frequently seen in men and tumors with high grade histology (solid or micropapillary-predominant pattern). In the stage IA cohort, patients with STAS showed significantly worse RFS compared to those without STAS [hazard ratio (HR) 2.01, 95% confidence interval (CI): 1.23–3.30, P=0.006]. Furthermore, RFS was similar between patients with stage IA tumors exhibiting STAS and those with stage IB tumors (HR 1.42, 95% CI: 0.95–2.14, P=0.091). This trend was also observed for OS. In multivariate analysis, STAS remained as an independent prognostic factor for worse RFS and OS in patients with stage I adenocarcinomas.

The investigators next divided the stage IA cohort into four groups per tumor size (≤2 cm or >2–3 cm) and STAS status (presence or absence). In patients with adenocarcinomas >2–3 cm, STAS was associated with significantly shorter RFS (HR 2.36, 95% CI: 1.16–4.80, P=0.017) and OS (HR 3.94, 95% CI: 1.80–8.63, P=0.001). Although STAS also showed a trend towards shorter RFS and OS in patients with adenocarcinomas <2 cm, the association was not statistically significant [RFS (HR 1.83, 95% CI: 0.91–3.69, P=0.091) and OS (HR 2.19, 95% CI: 0.94–5.10, P=0.072)]. In addition, there was no significant difference in RFS (HR 0.96, 95% CI: 0.51–1.83, P=0.912) and OS (HR 0.90, 95% CI: 0.42–1.92, P=0.784) between patients with tumors ≤2 cm and STAS present and those with tumors >2–3 cm without STAS. Further, there was no difference in RFS (HR 0.95, 95% CI: 0.55–1.64, P=0.842) and OS (HR 0.67, 95% CI: 0.36–1.24, P=0.205) between patients with tumors >2–3 cm and STAS present and those with stage IB tumors.

Their findings raise the possibility that STAS could be included as a part of T staging parameters in lung adenocarcinomas since the prognosis of patients with adenocarcinomas <2 cm [T1a, based on American Joint Committee on Cancer, 7th edition (11)] exhibiting STAS is similar to that with adenocarcinomas >2–3 cm (T1b) and no STAS, while the prognosis of patients with adenocarcinomas >2–3 cm (T1b) and STAS is similar to that with stage IB adenocarcinomas.

There remain, however, three questions to the study of Dai *et al.* (10). First and foremost is that visceral pleural invasion and lymphovascular invasion were not assessed individually in their study. STAS has been found to be associated with the presence of pleural invasion and lymphovascular invasion in several studies (9,12,13). In addition, the presence of pleural invasion and lymphovascular invasion are important prognostic factors in small adenocarcinomas (14). These factors should be included in a multivariate analysis for survival.

Second, the possible effects of adjuvant chemotherapy on prognosis were not considered. In their study, 154 of 383 (40.2%) patients with stage IA adenocarcinomas including 71 of 116 (61.2%) with STAS received adjuvant chemotherapy. The Japan Lung Cancer Research Group on Postsurgical Adjuvant Chemotherapy (15) performed a phase 3 trial, in patients with completely resected pathologic stage I adenocarcinomas, comparing oral uracil-tegafur (250 mg of tegafur per $m^2$ of body-surface area per day) for 2 years without chemotherapy, and concluded that uracil-tegafur significantly improved survival after complete resection. Interestingly, benefits from adjuvant chemotherapy depend on the histologic subtype of lung adenocarcinoma. Tsao *et al.* (16) analyzed 1,766 patients from several adjuvant chemotherapy clinical trials for lung adenocarcinomas, and showed that patients with solid and micropapillary-predominant adenocarcinomas experienced the most benefits from adjuvant chemotherapy. Given that patients with solid and micropapillary-predominant adenocarcinomas reportedly have a high prevalence of STAS (6,8,9), adjuvant chemotherapy might have affected the results of the study by Dai *et al.* (10). Therefore, subgroup analyses for STAS in patients with or without adjuvant chemotherapy are warranted.

Third, there have been conflicting reports on the prognostic significance of STAS in lobectomy *vs.* limited resection. Kadota *et al.* (6) showed that the presence of STAS increased a risk of recurrence in patients who had undergone limited resection, but not in those with lobectomy, while some studies reported the similar, negative prognostic impact of STAS in patients with lobectomy (9,13). In the study by Dai *et al.*, the type of surgery may have limited impact on prognosis, since 95% of the patients had undergone lobectomy. An assessment on the prognostic impact of SATS in the subgroup of patients with lobectomy would have been insightful, however.

Although several studies have shown that STAS is a marker of worse prognosis in resected lung adenocarcinomas, it is worth noting that some of the observed STAS may have been artifacts made during sectioning of lung resection specimens. Thunnissen *et al.* (17) named this phenomenon spreading through a

 

knife surface (STAKS). Blaauwgeers *et al.* (18) performed a prospective, multi-institutional study to confirm the concept of STAKS, and concluded that about 90% of the floating tumor cells and clusters ("STAS") could be explained by mechanical artifacts made by blades/knives. In contrast, Yagi *et al.* (19) performed a 3D reconstruction analysis and showed that most STAS were not 'free-floating', but rather, attached to alveolar walls. They concluded that most STAS were not artifacts, but a non-contiguous spread form. Thus, the concept of STAS is still debatable. However, given that STAS is one of several independent prognostic factors, including the histologic subtype of lung adenocarcinoma and tumor stage, the presence of single or clusters of tumor cells in air spaces away from the tumor boundary is likely indicative of aggressive biology of the tumor, irrespective of how they are generated.

In conclusion, the study by Dai *et al.* (10) is the first to demonstrate the influence of STAS on staging. This is an important advancement in the research of STAS, and if additional, large scale studies confirm their findings, inclusion of STAS as a parameter of lung cancer staging may be considered.

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## Footnote

*Conflicts of Interest*: M Mino-Kenudson serves as a consultant for Merrimack Pharmaceuticals and H3 Biomedicine, and as an advisory board member for Roche. H Uruga has no conflicts of interest to declare.

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