Editorial

Tumor spread through air space, the clinical implications for T factor and effects on the disease recurrence and prognosis

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The findings for the tumor spread through air space (STAS) in lung adenocarcinoma were reported by Kawakami *et al.* (1) and have attracted attention as unique clinical characteristics associated with a micropapillary pattern and nodal metastasis (1). In 2011, the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) revised the classification of lung adenocarcinoma to include the novel findings of molecular pathology as well as the correlation with clinical outcomes (2). STAS was clearly recognized as a novel invasive morphology defined as a micropapillary clusters, solid nests, or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma (3). The latest WHO Classification of Tumors of The Lung, Pleura, Thymus and Heart 4th Edition in 2015 (4) basically follow the IASLC/ATS/ERS classification. STAS is often discussed in lung adenocarcinoma, especially in association with a micropapillary pattern, and is known to influence a poor outcome, even with early stage disease (5,6). STAS is recognized in approximately 30–50% of lung adenocarcinomas (5,6). Furthermore, recent publications have reported that STAS coexistence in squamous cell carcinoma was also associated with poor clinical outcomes after surgery (7,8).

Dai *et al.* from Shanghai Pulmonary Hospital recently reported in the *Journal of Thoracic Oncology* that the existence of STAS may be useful for more precisely stratifying the prognosis of resected lung adenocarcinoma (9). Tumors between 2–3 cm in size showed a worse prognosis than smaller ones, as no decreased survival was observed in tumors <2 cm in size (9). A total of 383 and 405 subjects with stage IA adenocarcinoma based on the 7th edition of TNM classification for lung cancer as proposed by the IASLC (tumor size <3 cm) were enrolled in this study as a study cohort and validation cohort, respectively. The predominant histologic subtype of adenocarcinoma was determined based on the IASLC/ATS/ERS classification (2), and the definition of STAS was the same as that used in a previous report (3). Two independent pathologists classified STAS into single-cell, micropapillary cluster, or solid nest-predominant subtypes, and the distance between the tumor margin and the furthest STAS was also measured.

Dai *et al.* observed STAS in 116 (30.3%) subjects in the study cohort and 127 (31.4%) subjects in the validation cohort, and STAS was more frequently observed in male patients and in coexistence with high-grade histologic adenocarcinoma, such as micropapillary or solid subtype. The maximum estimated distance between the tumor margin and the furthest STAS was 1.35 cm in the study cohort and 0.87 cm in the validation cohort. These results were compatible with the findings of a previous report by Kadota *et al.* that reviewed resected small (≤2 cm) adenocarcinomas (10). Those authors showed the risk of developing locoregional as well as distant recurrence in STAS-positive small lung adenocarcinomas treated

with limited resection; however, the risk was hedged by performing lobectomy (10). Dai *et al.* complemented Kadota *et al.*'s report, revealing a decreased survival in STAS-positive adenocarcinomas 2–3 cm in size in a cohort in which the majority of the subjects underwent lobectomy (9). Both the recurrence-free and overall survival curves of STAS-positive adenocarcinomas 2–3 cm in size were similar to those of stage IB disease (adenocarcinoma between 3–7 cm in size) (9). Interestingly, we reported a similar phenomenon for the analysis of lung adenocarcinoma with a micropapillary pattern (11). In our analysis, the recurrence-free survival curve of adenocarcinoma with a micropapillary pattern was equivalent to that of T2 adenocarcinoma without a micropapillary pattern, and the recurrence-free survival curve of adenocarcinoma with a micropapillary pattern as well as STAS was equivalent to that of T3 adenocarcinoma without a micropapillary pattern (11).

Dai *et al.* did not discuss the recurrence pattern in their analysis (9). Regarding recurrence patterns, it is easy to imagine the increased incidence of surgical stump recurrence in limited surgery cases due to an insufficient margin between the resection line and the STAS (12,13). The adequate resection margin has been discussed, and a distance exceeding the main tumor diameter is generally recommended (14). Therefore, achieving an adequate surgical margin is considered to be applicable for STAS-positive lung cancers, and this has also been established in previous reports (9-11). Anatomical lobectomy should be selected for STAS-positive cases, and the careful confirmation of the lack of tumor cells in the surgical stump during surgery is warranted for patients who undergo limited resection for clinical reasons. The appropriate application of techniques for examining the margin cytology might help resolve this issue (15). The positivity of nodal metastasis is another important factor influencing locoregional recurrence. Warth *et al.* reported the STAS was significantly associated with nodal metastasis (6). In our retrospective analysis, 15 out of 31 (48.4%) STAS-positive cases showed nodal metastasis (11). On reviewing the radiological findings of our cases, 7 out of 15 (46.7%) cases showed no nodal enlargement (<10 mm in the short axis) on chest CT as well as no abnormal accumulation of ^{18}F-fluoro-deoxyglucose on positron emission tomography (PET) (*Figure 1*). Such cases with radiologically normal lymph nodes (both CT and PET negative) could be waived for any invasive nodal staging modalities, including mediastinoscopy or ultrasound-guided procedures according to the current guidelines for nodal staging in patients with lung cancer (16). The difficulty of obtaining accurate preoperative nodal staging increases the risk of not only occult N2 disease but also inappropriately selecting limited surgery.

The increased incidence of distant recurrence in STAS-positive lung cancer is another important issue. The unique and aggressive features of STAS have been shown to be associated with an increased incidence of lymphatic invasion and vascular invasion (10). A previous report showed a higher incidence of recurrence in resected stage IA non-small cell lung cancer with lymphovascular invasion than in subjects without lymphovascular invasion (17). However, the efficacy of adjuvant chemotherapy for stage IA adenocarcinoma has not been established. Indeed, 60% of patients received postoperative chemotherapy in Dai *et al.*'s cohort, even for the stage IA disease, but there was no significant benefit to the clinical outcome (9). Regarding the biomarkers of STAS-positive adenocarcinoma, an increased incidence of *KRAS* (5) and *BRAF* (6) mutations and a decreased incidence of epidermal growth factor receptor (EGFR) mutations (5,6,12) have been reported. This was compatible with the findings that patients with STAS are more likely to be male and smokers and to have high-grade adenocarcinoma subtypes (5,12). The genetic mechanism underlying the development of STAS by lung cancer and its relationship with aggressive invasiveness have yet to be clarified. The poor prognosis of micropapillary predominant adenocarcinoma, which is a major morphologic subtype, accompanied by STAS might be associated with mesenchymal-epithelial transition factors, as suggested by a recent publication (18). Novel treatment strategies are needed for STAS-positive patients, such as adjuvant therapy with immunocheckpoint inhibitors (19).

Diagnosing the subtypes of lung cancer is important for appropriate surgical planning; however, diagnosing STAS preoperatively or even during thoracotomy is still challenging. Attempts at detecting STAS by airway secretion cytology (20) or frozen sections during surgery (21) have been encouraging, but a number of limitations associated with high-sensitivity detection have been reported in real-world clinical settings. As mentioned above, STAS-positive lung cancer is frequently accompanied by high-grade adenocarcinoma, especially that with the micropapillary pattern (22), or squamous cell carcinoma (7,8). These tumors tend to be visualized as solid nodules on computed tomography and demonstrate a high maximum standardized

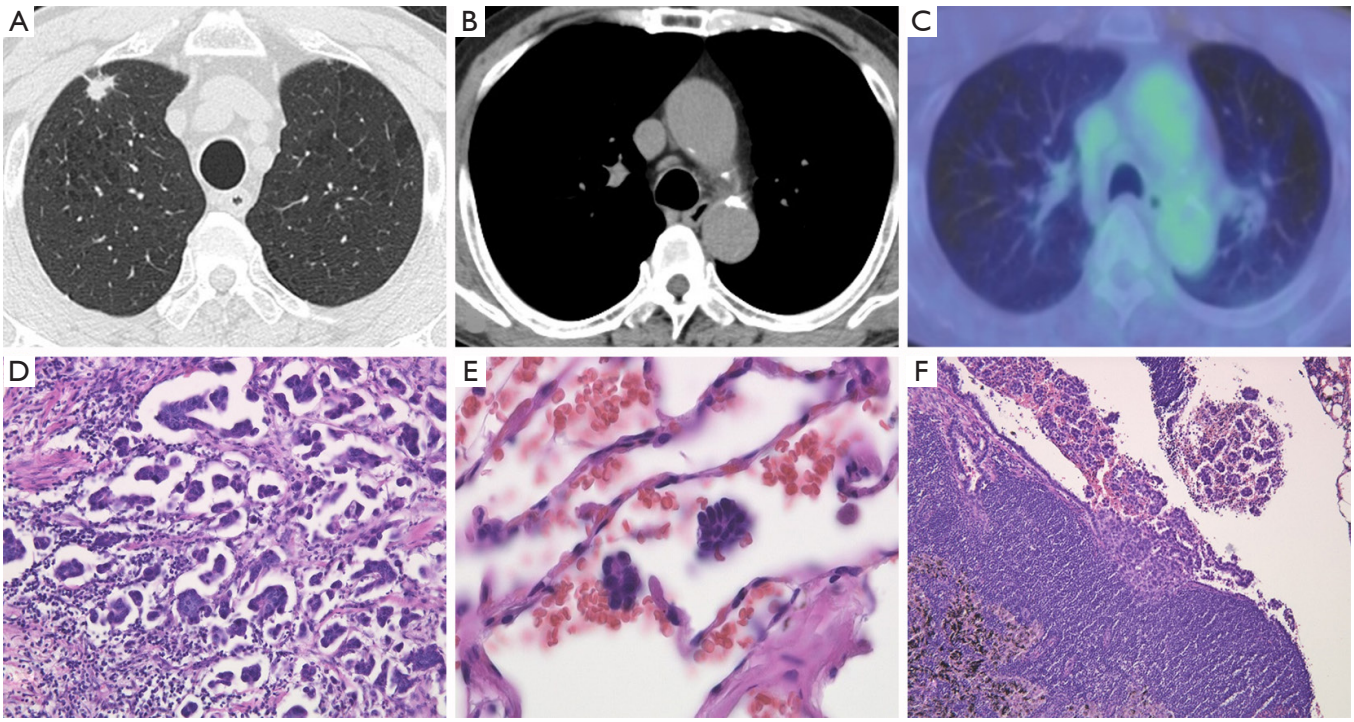

Figure 1 Lung cancer in the right upper lobe with occult mediastinal lymph node metastasis. (A) Small pulmonary nodule in the right upper lobe; (B) no enlargement on station 4R; (C) no abnormal accumulation of FDG on station 4R; (D) main tumor was diagnosed as micropapillary predominant adenocarcinoma (H&E staining; magnification 100×); (E) STAS was found in the adjacent alveolar space (H&E staining; magnification 400×); (F) micrometastasis was revealed in the station 4R (H&E staining; magnification 40×). FDG, fluorodeoxyglucose; STAS, spread through air space.

uptake value on PET (23,24). When we encounter tumors with radiological features suggestive of STAS-positive lung cancer (21), we should avoid limited surgery because of the increased risk of recurrence (25).

In conclusion, Dai *et al.* reported that the presence of STAS was associated with a worse recurrence-free as well as overall survival in patients with stage I lung adenocarcinoma, especially for tumors 2–3 cm in size, which are currently categorized as T1c by the 8th edition of Lung Cancer TNM classification system. The survival curve was equivalent when the T factor was upgraded one level over the original one in each case. STAS is a novel concept of tumor invasion and should be routinely reported by pathologists to clinical doctors, as it drastically affects the clinical outcome. Whether or not STAS should be included in the T factor classification should be discussed in the next revision of the TNM classification system. STAS is not a rare finding and is important to consider when deciding on proper treatment strategies, especially for surgery. We need to establish better ways of categorizing patients more precisely, and Dai *et al.* remind us of the importance of clinical studies in lung cancer clinics.

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Footnote

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