Editorial

Spread through air spaces (STAS): prognostic impact of a semi-quantitative assessment

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Following validation in two large independent cohorts from the US and Germany (1,2), the concept of spread through air spaces (STAS) was introduced for pulmonary adenocarcinomas (ADC) in the 2015 World Health Organization (WHO) Classification for lung cancer and subsequently validated and extended (3). Now, Uruga *et al.* provided evidence that a semi-quantitative assessment of STAS might provide additional prognostic information (4).

According to the 2015 WHO Classification, STAS is defined as "micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor". Besides the existing criteria for invasion (a histological subtype other than a lepidic pattern; myofibroblastic stroma associated with invasive tumor cells; vascular or pleural invasion), STAS was thereby established as a fourth category which defines invasion for ADC.

Early reports already indicated that erogenous tumor spread and free floating cell clusters from ADC but also metastases from colorectal cancer are unfavorable prognostic features (5-7). Onozato *et al.* described so-called tumor islands and their adverse prognostic impact, a morphological feature closely related to STAS in 2013 (8). 3D reconstructions revealed that tumor islands are connected to the main tumor at different levels (9). Tumor islands were significantly associated with a worse recurrence-free survival (8).

The concept of STAS was initially validated by two large simultaneous publications (1,2). In a series of 411 stage I ADC it was demonstrated that STAS is a phenomenon usually found in the first alveolar layers close to the tumor but occasionally can be found more than 50 alveolar spaces away from the main tumor. STAS was significantly associated with lymphovascular invasion and high-grade histological pattern (1). The association of STAS to lymphovascular invasion was subsequently validated (10). In a series of 569 ADC STAS was significantly associated with male sex, lymph node and distant metastasis, tumor stage, and high-grade histological patterns (2). Further correlations were found with *KRAS* and *BRAF* mutations (2). Another recent study concerning STAS in a series of 318 stage I ADC confirmed and extended the yet available data. The authors found significant associations of STAS with the male sex, the median CEA level, smoking status, median maxSUV, solid nodules on computed tomography, p-stage, *EGFR* wild-type, lymphovascular invasion, and pleural invasion (11). In the series by Uruga *et al.* where STAS was semi-quantitatively analyzed in 208 stage I ADC there were statistically significant associations between higher STAS and solid predominant ADC, pleural invasion, lymphatic invasion, vascular invasion, and tumor size ≥10 mm (4). In this study STAS was arbitrarily categorized as low STAS (1–4 single cells or clusters) and high STAS (>5 single cells or cell clusters). About 52.4% of the cases had no STAS, 18.3% low STAS, and 29.3% high STAS. For the assessment all tumor edges were screened and then STAS

was analyzed in 1-3 selected fields with most prominent STAS.

By analyzing a series of 445 stage I–III lung squamous cell carcinomas (SCC), Lu *et al.* demonstrated for the first time that STAS is not limited to ADC but is also a significant prognostic parameter for SCC (12).

Of note, one of the first validation studies on STAS found different survival rates depending on the type of the resection. Whereas STAS was not significantly associated with recurrence in the lobectomy group it was a significant prognosticator for any as well as locoregional recurrence in the limited resection group (1), pointing towards the potential clinicopathological impact of this new feature. In the second validation study, STAS was a significant prognosticator for both overall and disease-free survival even in patients with lobectomy and independent of the extent of STAS. Furthermore, STAS remained a worse prognosticator in multivariate analysis including the predominant pattern but not independent of stage (2). Although the analyzed subgroups were small, this study also demonstrated for the first time that the presence of STAS adds significant prognostic information to the predominant pattern (2), which was further underlined by a subsequent study focusing on the papillary pattern (13). The additive prognostic value of STAS to histological patterns was confirmed by a retrospective study of ADC with a micropapillary component in which the prognostic impact of free tumor cell clusters was analyzed (10). There was a significant association with recurrence-free survival and mortality (10). More interestingly, the authors demonstrate that the presence of a micropapillary component together with STAS results in a shift of the T stage compared to the same tumors without both features being present. In a further validation study STAS was confirmed as an independent prognostic parameter in multivariate analysis for both overall and recurrence-free survival (11). In a series of 544 ADC with a validation cohort of 541 patients, those with ADCs 3 cm or smaller and STAS had worse recurrence-free and overall survival than those without STAS. Comparable survival rates were observed in patients with stage IA with STAS present and those with stage IB ADC. Multivariate analysis revealed STAS to be an independent prognostic factor in ADC 3 cm or smaller. Among patients with ADC larger than 2 to 3 cm, STAS still stratified the prognosis. Moreover, the unfavorable prognosis of patients with ADC larger than 2 to 3 cm with STAS present was similar to that of patients with stage IB ADC (14).

With the approach by Uruga *et al.* to semi-quantitatively analyze STAS there was a significant association between high STAS in the tumor periphery and shorter recurrence-free survival in univariate analysis. In multivariate analysis, STAS remained a significant predictor of survival (4). The incidence for recurrence was 2% for no STAS, 5% for low STAS, and 21% for high STAS. This points out that, although the distance of STAS from the main tumor does not seem to be of high prognostic relevance in neither for ADC nor SCC (2,12,14), the quantity of STAS might be an important prognostic parameter. Further studies are needed where STAS is analyzed quantitatively to further narrow in on this and to potentially define clinically meaningful cut-offs.

In SCC the cumulative incidence of any, distant, and locoregional recurrence as well as lung cancer-specific death were significantly higher in patients with STAS compared to those without, and these associations remained significant in multivariate analyses. As demonstrated in ADC (2) the extent of STAS was not relevant for prognosis (12). The prognostic impact of STAS in SCC was most recently confirmed in a series of 2016 cases from Japan (15). Thus, beyond budding and cell nest size which have previously been identified as prognostically relevant morphological parameters in SCC (16-19). STAS seems to be another morphological feature to allow for a better prognostic stratification of SCC and potentially the establishment of a clinically meaningful grading system in the near future.

An interesting point is that there are first data pointing towards that STAS might be a potential candidate to upgrade the T stage in order to improve the accuracy of the prognosis of early stage ADC. Eguchi *et al.* demonstrated that the 5-year cumulative incidence of recurrence and cumulative incidence of lung cancer–specific death in patients with ADCs 2 cm or smaller was stratified by STAS (20). This is further underlined by a large multinational cohort of >2,000 early stage ADC where STAS together with solid and micropapillary patterns were significant parameters for an optimized patient stratification based on respective nomograms (21).

Up to now all studies on STAS, despite different definitions, demonstrate that this novel morphologic feature is of high prognostic value. Thus, STAS should be included into pathological reports. However, it is still debatable whether STAS is an *in vivo* effect in any instances or potentially an artifact (22). With respect to a better separation of STAS from artificial floaters it was suggested to consider only tumor cells as STAS if they appear as detached small clusters within air spaces in a continuous manner from the edge of the tumor, and the distribution is consistent with the overall configuration of the circumferential tumor edge. Haphazardly distributed

fragments of tumor with sharp jagged edges might be regarded as artifacts (12). Within this context further studies are clearly warranted to better separate floaters from STAS and evaluate the potential prognostic impact of both. Another yet open question is if STAS can be reliably detected in frozen sections, the only option to directly impact the surgical procedure since STAS is not evident in preoperative imaging procedures. Up to now only sparse data are available in this context. Kameda *et al.* reported that STAS could be identified in frozen sections with a sensitivity, specificity, and accuracy of 71%, 92.4%, and 80%, respectively. Clearly these results have to be validated in subsequent studies (23).

In summary, STAS is associated with multiple pathologic and clinical features of aggressiveness in both SCC and ADC and is an important prognostic feature independent of tumor stage and ADC growth patterns. The data by Uruga *et al.* (4) indicate that a semi-quantitative assessment of STAS might provide additional prognostic information, which should be validated and extended in subsequent studies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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