Editorial Commentary

Lung neuroendocrine tumors: a new addition to the evolving list of spread through air spaces

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Air-filled spaces are a notable characteristic of the lung. When a cancer develops in the lung, it is often surrounded by air spaces; thus, there is the possibility that cancer cells spread thorough air spaces. In fact, Kodama and colleagues presented a lung cancer case with multifocal "aerogenous" spread in 1980 and ultrastructurally studied the nature of detached fragments (1). Since then, multiple groups have reported the aerogenous spread of lung cancer cells, but it was not until 2012 when systematic pathological and prognostic analyses of the aerogenous spread of lung cancer cells began conducted. Onozato and colleagues found unique island-like structures in two of four lung adenocarcinomas analysed by 3D reconstruction and named them as tumor islands (2,3). "Tumor islands" are detached, large clusters of tumor cells in alveolar spaces separated from the main tumor mass but are connected to the main tumor mass in different tissue levels (2). Subsequently, they showed the association of tumor islands with shorter recurrence-free survival in stage I–II lung adenocarcinomas and hypothesized that tumor islands represent 'air space invasion" (3). Kadota and colleagues demonstrated that the spread of single tumor cells or micropapillary/solid type tumor cell clusters within air spaces adjacent to the main tumor [i.e., tumor spread through air spaces (STAS)] is a significant risk factor for shorter recurrence-free survival in patients with small lung adenocarcinomas (≤2 cm) treated with sublobar resection (4). Of note, there appear to be mutual morphologic features between the solid type STAS, in particular, large clusters and tumor islands. Based on these results, STAS was recognized as a new form of invasion, "air space invasion," in the 2015 World Health Organization (WHO) classification and became an exclusion criterion for minimally invasive adenocarcinoma (5). Subsequently, Dai *et al.* showed no statistical difference in recurrence free survival between patients with stage IA lung adenocarcinoma harboring STAS and those with stage IB suggesting that STAS could be a staging factor (6). In addition, STAS has been seen not only in lung adenocarcinomas but also in squamous cell carcinomas (7-9) and pleomorphic carcinomas (10). Many subsequent studies reported STAS as a predictor of worse patient outcomes, and a systematic review and meta-analysis of 2,897 patients with non-small cell lung carcinoma showed that the presence of STAS was associated with shorter recurrence-free survival [hazard ratio (HR): 1.975; P<0.001] (11). More recently, Eguchi and colleagues conducted a propensity score matching analysis on lobectomy *vs.* sublobar resection for stage I lung adenocarcinoma and found shorter recurrence-free and overall survivals of the patients with STAS compared with those without in the sublobar resection cohort, while STAS had no bearing on patients' outcomes in the lobectomy cohort. In addition, the worse outcomes were irrespective of surgical margin-to-tumor diameter ratio in the STAS+ patients. Accordingly, they emphasized the importance of lobectomy for T1N0M0 lung adenocarcinomas with STAS opposed to sublobar resection (12). Thus, when STAS is identified in a sublobar resection specimen, even for a small node negative tumor, completion lobectomy may need to be considered. Interestingly, however, STAS has been shown to be predictor of worse outcomes in patients who underwent lobectomy for other types of lung cancer (7,8).

Although few studies have evaluated STAS and its biological significance in patients with small cell carcinoma (SCLC) and atypical carcinoid (AC) (13,14), no study has investigated the prognostic significance of STAS in a broad spectrum of lung neuroendocrine tumors (NETs) in a comprehensive manner. Given this background, Aly and colleagues examined a prognostic impact of STAS in lung NETs in a study involving 487 surgically resected stage I, II, and III tumors comprising 299 typical carcinoid (TC), 38 AC, 93 large cell neuroendocrine carcinoma (LCNEC), and 57 SCLC (15). In the study, STAS was defined as the presence of more than one floating tumor cell cluster at least one air space away from the tumor boundary, and continuous alveolar space spread from the tumor edge to the furthest STAS was also required. STAS was present in 129 of the 587 patients (22%), and, in univariable analysis, was associated with higher smoking pack-years, adjuvant chemotherapy, higher pathological stage, presence of lymphatic and vascular invasion, presence of necrosis, higher mitotic count, Ki-67 labeling index, and histologic subtype. The authors also analyzed the incidence and pattern of recurrence and showed a postoperative 5-year recurrence rate of 54% in patients with STAS and that of 24% in those without (P<0.001). Lung cancer-specific cumulative incidence of death (LC-CID) was also higher in patients with STAS than in those without (43% *vs.* 18%, P<0.001). Of note, the prognostic analyses were performed in only AC, LCNEC, and SCLC (n=188) due to the low recurrence rate in patients with TC. Upon multivariable regression analysis, STAS was associated with a higher recurrence rate (HR: 2.85; P<0.001) and higher LC-CID (HR: 2.72; P<0.001) irrespective of histologic subtypes. As for the pattern of recurrence, locoregional recurrence rates were not significantly different between patients with STAS and those without (P=0.8), while a distant recurrence rate was higher in patients with STAS (P=0.006). Further, the patients with STAS had a risk of brain metastasis three times greater than those without (18% *vs.* 5%, P=0.010), and lymph node and adrenal metastases were also more prevalent in patients with STAS than in those without (P=0.032 and P=0.020, respectively). In a subgroup analysis of patients with STAS, a higher incidence of brain metastasis was found in the LCNEC cohort (23% *vs.* 6%, P=0.035) but not in the SCLC cohort (19% *vs.* 7%, P=0.195).

The study by Aly and colleagues revealed some interesting findings (15). First, STAS was found to be a predictor of worse prognosis in lung AC, LCNEC and SCLC as well as in lung adenocarcinomas, squamous cell carcinomas, and pleomorphic carcinomas. Second, as for the site of recurrence, the incidence of brain metastasis was three times higher in patients with STAS than in those without, while, in the subclass analysis, STAS was a risk factor for brain metastasis only in the LCNEC cohort but not in the SCLC cohort. In previous studies, brain metastasis was found to be very frequent in lung LCNEC and SCLC, occurring in approximately 50% of cases (16), and prophylactic cranial irradiation (PCI) was able to reduce the risk in half in patients with SCLC, thus leading to the recommendation that the patient with limited-stage SCLC undergo PCI after a standard first-line chemotherapy (17). In the study by Aly and colleagues, 21% of SCLC and none of LCNEC patients received PCI (15), and this might have contributed to the difference in the brain recurrence rate between LCNEC and SCLC in the STAS+ group. Thus, it is reasonable to think that PCI may be beneficial for patients who are found to have LCNEC harboring STAS in lung resection as well as those with SCLC. The third interesting finding is that the recurrence pattern was different between adenocarcinoma and NETs when the tumor exhibits STAS. Kadota *et al.* originally reported that STAS was associated with increased risks of locoregional and distant recurrence in patients with small stage I lung adenocarcinoma who had undergone sublobar resection, but not in those who had undergone lobectomy (4). Aly *et al.* recently performed 3-dimensinal reconstruction of STAS in lung TC and AC, and have demonstrated a connection between STAS and the main tumor similar to tumor islands (18). These data may indicate some biological differences of STAS between adenocarcinoma and NE tumors or other types of lung cancer. In adenocarcinoma, single tumor cells, micropapillary and/or small clusters of tumor cells may travel far from the main tumor, and if tumor cells remain the remnant lung parenchyma after sublobar resection, they may become a nidus of tumor recurrence (19). In contrast, STAS in the other types of lung tumor including NETs that exhibits solid clusters (similar to tumor islands) may merely reflect the aggressive biology/invasive capability of the tumor.

Although multiple studies have contributed to improving our understanding of STAS and its biological significance, there remain several questions. The fundamental question is whether STAS is an *in vivo* phenomenon or an artifact, and this issue has long been under an intensive discussion. The phenomenon of floating tumor cells in alveolar spaces created artificially during processing at the pathology laboratory was named “spreading through a knife surface” (STAKS) by Thunnissen *et al.* (20). They have demonstrated in a multicenter study that the number of free tumor cell clusters within air spaces is increased by knife cuts, and 93% of the tumor cell clusters could be explained by mechanical forces associated with tissue handling (21). Many studies encompassing various histological types, however, have reproducibly shown STAS to be a risk factor for postoperative recurrence (4,6-11). Furthermore, as already discussed, large solid clusters of STAS/tumor islands have been proven to be a direct extension from the main tumor. Thus, it is reasonable to think that at least a part of STAS is real, and STAS in general reflects aggressive tumor biology irrespective of how it develops or is generated.

Nevertheless, it is important to confidently differentiate STAS from “true” artifacts (to prevent potentially unnecessary completion lobectomy in patients with adenocarcinoma). Unfortunately, however, the criteria for STAS have not been standardized yet and high concordance on the diagnosis of STAS by pathologists needs to be achieved. The multiple studies have employed various definitions of STAS including cut-offs for a number of tumor clusters/cells and/or distance from the main tumor (22). For instance, Morimoto and colleagues defined STAS as more than 3 clusters containing <20 nonintegrated micropapillary tumor cells located >3 mm away from the main tumor to differentiate STAS from artifacts (23). In the current study (15), Aly and colleagues described several features of artifacts as exclusion criteria of STAS: (I) mechanically dissociated tumor floaters (clusters of tumor cells with a ragged-edge, located randomly and/or located at the edge of the tumor section); (II) normal benign pneumocytes or bronchial cells; (III) strips of tumor cells detached from alveolar walls or stroma due to poor preservation; (IV) isolated tumor clusters distantly situated away from the tumor not in a continuous manner. They also considered the presence of a single focus of STAS in the entire tumor as an artifact. In another study by Uruga and colleagues, a semi-quantitative assessment of STAS in patients with resected adenocarcinoma showed that high STAS (≥5 clusters of STAS in one 200× microscopic field) was associated with shorter recurrence-free survival compared to no STAS, but that low STAS (1–4 clusters of STAS in one 200× microscopic field) was not (24). Thus, while 5 or more clusters of STAS may be relevant in terms of survival, the significance of a few (2-4) clusters of STAS remains uncertain. As for the reproducibility of STAS among pathologists, in the study by Monroig-Bosque and colleagues, the diagnosis of STAS in 30 adenocarcinomas with significant micropapillary pattern varied from 34.1% to 52.8% (mean 43.4%) among 15 pulmonary pathologists (25). Further large-scale studies are warranted to elucidate and improve the reproducibility of the STAS diagnosis by pathologists.

In summary, Aly *et al.* (15) found STAS to be a poor prognostic factor in lung NETs (AC, LCNEC and SCLC). Furthermore, brain metastasis occurred more frequently in patients with STAS than in those without. These results might be useful for the postoperative management of patients with lung NET. Although our understanding of STAS and its prognostic significance in lung cancer has significantly advanced in the last few years, there remain multiple questions about STAS. Thus, further studies are warranted to address these questions.

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Footnote

Conflicts of Interest: M Mino-Kenudson serves as a consultant for Merrimack Pharmaceuticals and H3 Biomedicine. H Uruga has 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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