Editorial

Spread through air spaces—novel pattern of cancer progression

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Despite the proliferation of antismoking campaigns and lung cancer screening by computed tomography, lung cancer remains the leading cause of cancer death worldwide. Because of the anatomical features of the lung, the growth patterns of lung malignancies differ from malignancies of other sites. The patterns of lung cancer progression are cancer spread via vascular, lymphatic, or alveolar spaces (1). These are related to the biological behavior of the lung tumor. Regarding lung cancer prognosis, histopathological findings that include grade of differentiation (2), pleural invasion (3,4), and lymphovascular invasion (5,6) have been reported to be prognostic factors. The spread of lung cancer to the alveolar spaces was recently reported as a novel pattern of cancer progression, and reports on lung adenocarcinoma have shown that cancer spread through the air spaces (STAS) is a significant risk factor for recurrence and a poor prognostic factor for overall survival (1,7-15) (*Table 1*). As an aggressive manifestation of lung cancer, STAS was introduced as a new concept for lung adenocarcinoma in the 2015 World Health Organization (WHO) classification (16). WHO classification defined STAS as "micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor" (16).

The 1995 Atlas of Tumor Pathology recognized aerogenous spread as the presence of isolated clusters of tumor cells in the alveolar space (17), but at that time, aerogenous spread was underrated and had not been well studied. In 2015, Kadota *et al.* revealed that STAS was a significant risk factor for recurrence in patients with ≤2-cm stage I lung adenocarcinoma who underwent limited resection, wedge resection, or segmentectomy (8). Interestingly, they also showed that STAS was not related to recurrence in patients who underwent lobectomy. Onozato *et al.* reported that patients with lung adenocarcinomas and tumor islands (alternative term for "STAS"), which are large clusters of tumor cells in alveolar spaces, had a significantly worse prognosis than patients with lung adenocarcinomas without tumor islands (7). They showed that adenocarcinomas with tumor islands were more likely to be found in smokers, to show predominant solid or micropapillary growth patterns, and tended to have *KRAS* mutations. Furthermore, Warth *et al.* evaluated 569 resected lung adenocarcinomas and found that 288 of them (50.6%) showed STAS. They found that STAS was detected at high rates in men and in patients with adenocarcinomas with wild-type epidermal growth factor receptors, lymph node metastasis, distant metastasis, and advanced-stage lung cancer (1). Morimoto *et al.* investigated adenocarcinomas with a micropapillary component and studied the relationship between free tumor cell clusters and outcome (9). Instead of the term "STAS", they described "free tumor clusters (FTC)" and explained that FTC did not contain solid nests or single cells. Locoregional recurrence was frequently observed in patients with FTC and in those patients with shorter recurrence-free survival. They concluded that FTC had a negative impact on the postoperative outcome of patients with micropapillary-positive adenocarcinomas.

STAS is related to recurrence and survival in patients

Table 1 Studies on STAS and features similar to STAS in lung cancers

First author	Year	Objective	No. of patients	Findings of STAS positive cases
Onozato (7)	2013	Stages I–II, Ad	261	Lower RFS, no relationship with RFS in wedge resection
Kadota (8)	2015	Stage I, Ad	411	Risk of recurrence in limited resection
Warth (1)	2015	Stages I–IV, Ad	569	Lower OS and RFS
Morimoto (9)	2016	Stages I–III, Ad	67	Lower OS and RFS
Shiono (10)	2016	Stage I, Ad	318	Lower OS and RFS, risk of local recurrence
Lu (11)	2017	Stages I–III, Sq	445	Lower cancer-specific survival, no relationship with OS, risk of local recurrence and distant metastasis
Uruga (12)	2017	Stage I, Ad	208	Lower OS and RFS
Dai (13)	2017	Stage I, Ad	554	Lower OS and RFS, risk of local recurrence and distant metastasis.
Kadota (14)	2017	Stages I–IV, Sq	216	Lower RFS, risk of local recurrence and distant metastasis, lower RFS in lobectomy
Masai (15)	2017	All histology	508	Wedge resection cases, risk of local recurrence, no relationship with distant metastasis

STAS, spread through air spaces; Ad, adenocarcinoma; Sq, squamous cell carcinoma; OS, overall survival; RFS, recurrence-free survival.

with squamous cell lung carcinoma. Lu *et al.* investigated 445 cases of surgically resected stages I to III squamous cell lung carcinoma and identified STAS in specimens from 30% of the patients (11). Although patients with STAS had higher rates of recurrence and cancer-specific death than patients without STAS, the difference in overall survival between patients with and without STAS was not significant. Kadota *et al.* investigated Japanese patients with squamous cell lung carcinoma and confirmed the results of Lu *et al.* (14).

With advances in the detection of small-sized lung cancers, the demands for surgical procedures such as limited resection, wedge resection, and segmentectomy have increased. In 1995, the Lung Cancer Study Group investigated small (≤3 cm) T1N0 lung cancers and found that limited resection was associated with a higher risk of recurrence than lobectomy (18), and that lobectomy provided superior outcomes compared with limited resection. Lobectomy has subsequently been regarded to be the standard surgical procedure for lung cancers.

Recurrence, especially locoregional recurrence, remains a serious concern with regard to the effectiveness of limited resection. An adequate margin and absence of residual tumor cells after surgery are mandatory for preventing locoregional recurrence. Yoshida *et al.* reported on three patients who developed recurrence at the surgical margins (19). These patients were participants in a trial of limited resection (20) for noninvasive type lung cancer with a good prognosis, but recurrent tumor developed at the surgical margins. To avoid recurrence at the surgical margin after wedge resection, the investigators washed the stapler cartridges used for the resection with 200 mL of saline solution, and the lavage fluid was examined cytologically (20). Examination of frozen sections of all the staple lines marking the surgical margin during surgery would not be realistic. Intraoperative cytological examination of lavage fluid is the only option for checking the surgical margin. The investigators suggested that cancer cells might spread along the airways or blood vessels (19). It is possible that, in the case with STAS, cancer cells might persist in surgical margin.

STAS could be associated with local recurrence after limited resection. Other investigators whose work was described earlier in this article (7,8,15) found that lobectomy reduced the risk of locoregional recurrence in patients with STAS. Masai *et al.* performed multivariate analysis that revealed that STAS and width of the surgical margin were significant risk factors of recurrence (15). Furthermore, they concluded that STAS and a <1-cm width of the surgical margin are significant risk factors for local recurrence in patients with early-stage lung cancer undergoing limited resection. The choice of lobectomy over limited resection for lung cancer might be supported by the STAS phenomenon.

The mechanisms involved in the spread of cancer cells to air spaces are largely unknown. In terms of cell connections, a cell adhesion molecule such as epithelial (E)-cadherin or ICAM is thought to be associated with STAS. However, the decreased expression of epithelial (E)-cadherin has been reported to be unrelated to STAS (21). STAS might occur as a result of a surgical procedure or tumor biopsy, which leads to disruption of the resected tumor by manipulation. To examine this hypothesis, we determined the proportions of patients who developed STAS after different surgical procedures. We could not find differences in the rates of STAS between surgical procedures (10). However, it is speculated that preoperative biopsy procedures might lead to STAS.

There is a possibility that STAS can occur as an artifact during the processing of surgical specimens for histopathological evaluation. One report described the concept of "spreading through a knife surface (STAKS)" (22). STAKS is considered to be an artifact resulting from specimen processing. Since, in general, the steps in processing tissues and making slides are not standardized or recorded, verifying that STAKS can lead to observations of STAS is difficult. Despite the opinions that STAS is an artifact, many recent reports have confirmed the significant effects of STAS on the recurrence of lung cancer and survival. Kadota *et al.* described detailed methods for differentiating STAS from alveolar macrophages and artifacts (8,14). Dai *et al.* used the methods of Kadota and found similar results (13). I think that STAS is not artifact.

Dai *et al.* have reported that patients with adenocarcinomas ranging in size from <2 to 3 cm that showed STAS had an unfavorable outcome similar to the outcome of stage IB patients with or without STAS. The differences between overall survival and recurrence-free survival in patients with ≤2-cm adenocarcinomas with and without STAS were not significant (13). The authors suggested that STAS might be a factor to include in a staging system. While the TNM classification categorizes the tumor into stages based on the anatomical extent of tumor, histopathological factors such as lymphatic, venous, and perineural invasion are included in staging systems (23). In lung cancer, pleural invasion is only the histopathological factor that affects the T factor. However, pleural invasion is difficult to diagnose by hematoxylin and eosin staining, and instead should be evaluated on tissue preparations stained for elastic tissues. By contrast, STAS can be diagnosed on routine preparations stained by hematoxylin and eosin, indicating that diagnosing STAS should be easier than diagnosing pleural invasion.

How do we use the results of STAS in lung cancer surgery? In patients with small, i.e., 3 cm or less in size, lung cancers, STAS should be investigated to rule out the use of limited resection. Thus, the preoperative diagnosis of STAS is critical for selecting surgical procedures. If STAS can be identified or predicted before surgery, limited resection, which leads to higher risk of recurrence in patients with STAS, should be avoided. However, the preoperative identification of STAS is challenging. Moreover, STAS identification on intraoperative frozen sections is difficult. A biopsy specimen during surgery that contains normal lung parenchyma including the tumor should be a requirement. At this point, if the patients who underwent limited resection are found STAS, meticulous radiological follow-up of recurrence is needed.

In conclusion, Dai *et al.* showed that patients with stage IA adenocarcinomas ranging in size from <2 to 3 cm showing STAS had an unfavorable outcome similar to the outcome of stage IB patients with or without STAS. If limited resection is performed for stage IA lung cancer, thoracic surgeons should rule out STAS irrespective of the tumor size.

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Footnote

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

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