Editorial

Tumor spread through air space (STAS) is an important predictor of clinical outcome in stage IA lung adenocarcinoma

Hui-Zi Chen[1,2,3], Erin M. Bertino[1,2], Kai He[1,2]

[1]The James Cancer Hospital and Solove Research Institute, Comprehensive Cancer Center, [2]Division of Medical Oncology, Department of Internal Medicine, [3]Hematology and Medical Oncology Fellowship Program, Department of Internal Medicine, The Ohio State University, Columbus, OH 43210, USA

Correspondence to: Kai He, MD, PhD. Biomedical Research Tower Rm 494, 460 W. 12th Avenue, The Ohio State University, Columbus, OH 43210, USA. Email: Kai.He@osumc.edu.

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Despite an expanding armamentarium of therapies in recent years, lung cancer remains the leading cause of cancer-related deaths globally (1). Approximately 80% of lung cancers diagnosed worldwide are classified as non-small cell lung cancer (NSCLC), with adenocarcinoma being the most common histologic subtype. Tumor spread through air spaces (STAS) has recently been recognized as an important pattern of tumor invasion in early stage lung adenocarcinoma (2). Indeed, multiple independent groups have determined STAS to have a significant prognostic impact on recurrence in patients with resected stage I lung adenocarcinoma (3-5).

In a recently published article in the *Journal of Thoracic Oncology*, Dai and colleagues at the Shanghai Pulmonary Hospital in Tongji University reported an association between the presence of STAS and decreased survival for patients with clinical stage IA lung adenocarcinoma >2 to 3 cm (6). Clinical staging was based on the 7th edition of TNM classification for lung cancer as proposed by the International Association for the Study of Lung Cancer. In this retrospective single-institution study, the medical records of 2,665 patients who underwent surgical resection at Shanghai Pulmonary Hospital between January 2009 and December 2010 were reviewed. In the study cohort (n=383), patients with lung adenocarcinoma 3 cm or less were selected and further stratified by size into ≤2 cm (T1a) and between 2–3 cm (T1b). Two blinded pathologists independently evaluated H&E stained tumor sections for the absence (–) or presence (+) of STAS, which was classified into three distinct morphologic subtypes including single cells, micro papillary clusters and solid nests. Patients who received neoadjuvant chemotherapy, had multiple primary lung cancers or adenocarcinoma *in situ*, or had either R1 (microscopic residual) or R2 (macroscopic residual) resections were excluded from their study. Follow-up period for the study ended on December 31, 2016. Finally, the authors included a validation cohort (n=405) through chart review and selection based on the same inclusion/exclusion criteria of additional patients who underwent surgical resection of early stage lung cancer between January 2011 and March 2012.

The results of this retrospective analysis by Dai and colleagues provide support for a role of STAS in further risk stratifying stage IA (T1bN0M0) lung adenocarcinoma. In both their study and validation cohorts, the presence of STAS in patients with stage IA (<3 cm) lung adenocarcinoma was associated with a significant decrease in recurrence free survival (RFS) and overall survival (OS). When stage IA patients were further classified by tumor size into T1a (≤2 cm) and T1b (2–3 cm), a statistically significant difference in survival (RFS and OS) was detected for T1b tumors but not for T1a tumors.

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Additional analyses demonstrated that patients with stage IA T1b adenocarcinoma having histopathologic evidence of STAS had similar survival rates as patients with stage IB (T2a, 3–5 cm) adenocarcinoma. Finally, multivariate analysis showed STAS to be an independent prognostic factor for poor RFS and OS in the study cohort whereas in the validation cohort, STAS was only predictive of RFS but not OS.

Interestingly, while others have shown STAS to have prognostic significance in patients who underwent limited resection (3), Dai *et al.* showed STAS to have prognostic value for patients who underwent lobectomies. The authors further concluded that given existing data from their group and others, STAS is closely correlated with poor survival outcomes independent of surgery types. Another important aspect of the study to note is the observation that two-thirds of the study cohort patients (n=229) received post-operative chemotherapy. Hazard ratio analysis ultimately revealed no statistically significant relationship between adjuvant chemotherapy and survival these patients. However, it is worth noting that in North America, the recommendation for stage IA NSCLC patients who received appropriate (R0) resection is no additional therapy, including adjuvant chemotherapy. This recommendation is in accordance with the most current National Comprehensive Cancer Network guidelines (7). Nonetheless, despite this slight discrepancy, Dai and colleagues demonstrate an overall compelling relationship between STAS and recurrence of stage IA lung adenocarcinoma in this retrospective single institution study. Additional information regarding local versus distant recurrence, especially given that most patients have undergone lobectomies rather than limited resections, will also be relevant to evaluate and may provide basic mechanistic insight into how STAS correlates with recurrence. For instance, is a specific morphologic subtype of STAS such as micropapillary cluster STAS, which was the predominant subtype in these patients (study cohort, 78%; validation cohort, 83%), associated with increased risk of local or distant recurrence?

Finally, in addition to lung adenocarcinoma, multiple groups, including Kadota and colleagues, have now reported STAS to be an independent predictor of RFS in patients with resected lung squamous cell carcinoma (SCC) (8,9). In contrast to the predominance of micropapillary clusters in adenocarcinoma, all 87 patients with resected SCC (stages I–IV) had the solid nest phenotype (8). Furthermore, patients with stage I STAS positive SCC had a statistically significant risk of distant recurrence (P=0.033). A trend for locoregional recurrence in patients with stage I STAS positive SCC was also observed (P=0.09) (8). It remains to be seen whether STAS may represent a significant pattern of invasion in the less common subtypes of NSCLC as well as small cell and large cell neuroendocrine tumors of the lung.

In conclusion, the results presented by Dai *et al.* suggest that a more precise pathologic staging system may be achieved by incorporating a systematic evaluation for the presence or absence of STAS in Stage IA lung adenocarcinoma. The 8th edition of Lung Cancer TNM classification system will soon be implemented globally. In this new classification system, stage I lung cancer will be further stratified into IA, IB, and IC. Further integration of histopathologic prognostic markers along with genomic data may lead to significantly more accurate risk stratification of this patient population to improve their clinical outcome. Indeed, massively parallel sequencing technologies have enabled comprehensive interrogation of the complex genomic landscape of NSCLC including adenocarcinoma and SCC (10-13). Recent large-scale, prospective sequencing studies such as Tracking Non-Small-Cell Lung Cancer Evolution through Therapy (TRACERx) have demonstrated significant intratumor heterogeneity of surgically resected NSCLC (14), which could be further explored as a prognostic marker of clinical outcome in early stage NSCLC. This most recent study performed by Dai and colleagues represents an important example of the ongoing collective effort to optimize risk stratification, staging and management of early stage, potentially curable lung cancer.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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