Is spread through alveolar spaces, the newly recognized pattern of invasion, a potential game changer in lung adenocarcinoma?

Sarina Bains, Prasad S. Adusumilli

Thoracic Service, Department of Surgery, Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY, USA
Correspondence to: Prasad S. Adusumilli, MD, FACS, FCCP. Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Email: adusumip@mskcc.org.

Lung adenocarcinoma, the most common histologic subtype of lung cancer, is detected at an early stage in 25% of cases. With the implementation of the new National Cancer Institute guidelines, which recommend low-dose CT screening of all high-risk smokers, the number of patients diagnosed with early-stage lung adenocarcinoma is expected to increase (1). Despite early detection, mortality from lung cancer continues to be the highest among all malignancies. As small lung nodules are detected more frequently, the role of surgical intervention and management for early-stage lung cancer will be of increasing interest to thoracic surgeons and oncologists.

During the past decade, the single most important factor determining clinical management and prognosis of patients with lung cancer has been the tumor-node-metastasis (TNM) staging system (2). The current gold standard for curative-intent treatment is anatomical resection by lobectomy and lymph node dissection (3). Wedge resection with negative margins (lung-preserving surgery) has been increasingly used to treat patients with peripheral lesions (4,5). Lung-preserving surgery has an added benefit for heavy smokers, as many of them have borderline lung function and would tolerate lobectomy resection poorly (6). Despite the use of curative resection, 20% to 25% of patients treated surgically for early-stage lung cancer experience recurrence within 5 years; therefore, the ideal type of resection for patients with early-stage lung adenocarcinoma remains the source of much controversy (7-9).

The application of the TNM staging system is limited as it only describes the anatomic extent of tumors but fails to include other parameters that can greatly improve our capacity to prognosticate the disease (10). This led to the development of a new, more applicable classification system for lung adenocarcinoma by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society. Tumors that were previously classified as well-differentiated or poorly differentiated are now identified on the basis of their histologic growth patterns: adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), lepidic, acinar, papillary, micropapillary, and solid. This system proposes that different histologic growth patterns can be used as stage-independent predictors of survival (11). It has also been shown to be a powerful tool for stratifying patients with stage I lung adenocarcinoma into three prognostic groups: low-grade (AIS, MIA, and lepidic), intermediate-grade (acinar and papillary), and high-grade (micropapillary and solid) (12). Of these patterns, the high-grade subtypes, micropapillary and solid appear to demonstrate different patterns of spread. Tumors displaying any presence of the micropapillary subtype have been shown to have high rates of locoregional recurrence when treated with limited resection, despite the achievement of negative margins (7). Solid predominant tumors, conversely, tend to present with increased recurrence at distant sites (13). Knowing that different histologic subtypes are prone to recurrence at different sites suggested that a new type of invasion may be present, one that had not yet been identified.

Locoregional recurrence patterns following limited resection for small lung adenocarcinoma prompted pathologists to re-review slides, first to confirm that the

Page 2 of 3

Bains and Adusumilli. Lung adenocarcinoma spread through air spaces

tumor margins were in fact negative for tumor cells, and then to evaluate areas adjacent to the tumor margin. These areas were previously considered irrelevant, as they were extratumoral alveoli. Interestingly, clusters of viable tumor cells were identified at a distance from the tumor margin within the alveolar spaces.

A review of the literature revealed, with some surprise, that several other groups had also discovered viable tumor cells within the alveoli. Onozato *et al.* initially described tumor islands within alveolar spaces and showed that the presence of tumor islands was associated with an almost 2-fold higher risk of recurrence and worse prognosis (14). They also demonstrated that tumor islands were interconnected to each other, as well as to areas adjacent to the main tumor (15). This concept has also been described by radiation therapists, who recognized "microscopic extensions" of tumors—these extensions affected the clinical target volume and therefore affected the ability to deliver an accurate radiation dose (16,17). Recently, Gaikwad *et al.* described aerogenous spread as a new potential pathway for metastatic spread of lung adenocarcinoma. They reported the radiologic and pathologic features that can distinguish aerogenous metastases from lymphatic and hematogenous ones, by emphasizing the predominance of aerogenous spread in airspaces, with a lack of vascular or lymphatic invasion on pathologic review (18). Despite the awareness that this feature exists, the clinical implications of its presence were not well understood.

To prompt uniform reporting and evaluation, our group, for the first time, coined the term tumor spread through air spaces (STAS), which is defined as the spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor (19). STAS has been implicated in three morphologic patterns: micropapillary, solid nests or tumor islands, and single cells. Although the prognostic implications of STAS are still under investigation, STAS-positive tumors have a significantly higher risk of both locoregional and distant recurrence in patients undergoing limited resection, whereas patients undergoing lobectomy for STAS-positive tumors showed no significant difference (19). Warth *et al.* show that micropapillary predominant adenocarcinomas have the highest rate of STAS and correlate with worse overall and disease-free survival (20). These findings suggest that occult tumor cells within the air spaces are perhaps being left behind in limited resections, creating a virtual positive margin previously not identified

by pathologic examination. This explains the increased risk of both locoregional and distant recurrence. The data suggest lobectomy should be investigated as the treatment of choice for both STAS-positive and micropapillary lung adenocarcinomas, and they support the theory that STAS represents a new pattern of invasion in lung adenocarcinoma.

Given the prognostic implications of STAS in lung adenocarcinoma reported by multiple groups, its recognition can significantly impact clinical decision-making. Preoperative radiologic identification of STAS-positive tumors would provide surgeons with the information needed to choose lobectomy over limited resection. This would preclude the need for adjuvant therapy or re-resection, an operation necessary to avoid recurrence in STAS-positive patients who initially underwent limited resection. Unfortunately, the precise radiologic parameters to identify the presence of STAS have not been established. There are no studies investigating the intraoperative recognition of STAS. Postoperative microscopic identification of STAS should be standard practice in early-stage lung adenocarcinoma. This new pattern of invasion has been overlooked because the presence of cells within air spaces has previously been considered artifact and, thus, dismissed. Training pathologists to look beyond surgical margins to identify STAS, especially in cases where limited resection was performed will be of importance.

In conclusion, STAS is a pattern of invasion that is unique to lung adenocarcinomas, and it holds significant prognostic implications for both recurrence and overall survival. The involvement of STAS in other histologic subtypes of lung cancer has also yet to be evaluated. STAS is a novel prognostic tool for lung adenocarcinoma and should be utilized for its diagnostic potential.

Acknowledgements

Footnote

Provenance: This is a Guest Editorial commissioned by the Section Editor Jianfei Shen, MD (Department of Thoracic Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

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

References

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
2. Edge SB, Byrd DR, Compton CC, et al. American Joint Committee on Cancer Cancer Staging Manual. 7th ed. New York, NY: Springer; 2009:253-70.
3. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
4. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg 2010;251:550-4.
5. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer<=1 cm in size: a review of SEER data. Chest 2011;139:491-6.
6. Okada M, Koike T, Higashiyama M, et al. Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study. J Thorac Cardiovasc Surg 2006;132:769-75.
7. Nitadori J, Bograd AJ, Kadota K, et al. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. J Natl Cancer Inst 2013;105:1212-20.
8. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. Mod Pathol 2011;24:653-64.
9. Kadota K, Villena-Vargas J, Yoshizawa A, et al. Prognostic significance of adenocarcinoma in situ, minimally invasive adenocarcinoma, and nonmucinous lepidic predominant invasive adenocarcinoma of the lung in patients with stage I disease. Am J Surg Pathol 2014;38:448-60.
10. Rami-Porta R, Asamura H, Goldstraw P. Predicting the prognosis of lung cancer: the evolution of tumor, node and metastasis in the molecular age-challenges and opportunities. Transl Lung Cancer Res 2015;4:415-23.
11. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-85.
12. Sica G, Yoshizawa A, Sima CS, et al. A grading system of lung adenocarcinomas based on histologic pattern is predictive of disease recurrence in stage I tumors. Am J Surg Pathol 2010;34:1155-62.
13. Ujiie H, Kadota K, Chaft JE, et al. Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival. J Clin Oncol 2015;33:2877-84.
14. Onozato ML, Kovach AE, Yeap BY, et al. Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. Am J Surg Pathol 2013;37:287-94.
15. Onozato ML, Klepeis VE, Yagi Y, et al. A role of three-dimensional (3D) reconstruction in the classification of lung adenocarcinoma. Stud Health Technol Inform 2012;179:250-6.
16. van Loon J, Siedschlag C, Stroom J, et al. Microscopic disease extension in three dimensions for non-small-cell lung cancer: development of a prediction model using pathology-validated positron emission tomography and computed tomography features. Int J Radiat Oncol Biol Phys 2012;82:448-56.
17. Grills IS, Fitch DL, Goldstein NS, et al. Clinicopathologic analysis of microscopic extension in lung adenocarcinoma: defining clinical target volume for radiotherapy. Int J Radiat Oncol Biol Phys 2007;69:334-41.
18. Gaikwad A, Souza CA, Inacio JR, et al. Aerogenous metastases: a potential game changer in the diagnosis and management of primary lung adenocarcinoma. AJR Am J Roentgenol 2014;203:W570-82.
19. Kadota K, Nitadori J, Sima CS, et al. Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015;10:806-14.
20. Warth A, Muley T, Kossakowski CA, et al. Prognostic Impact of Intra-alveolar Tumor Spread in Pulmonary Adenocarcinoma. Am J Surg Pathol 2015;39:793-801.