Spread through alveolar spaces: An aerogenous invasion in pulmonary adenocarcinomas

Prasad S. Adusumilli, MD, FACS, FCCP

From the Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY. P.S.A.'s laboratory research is supported by grants from the National Institutes of Health (R21 CA164568-01A1, R21 CA164585-01A1, U54 CA137788, P30 CA008748, and P50 CA086438-13), the U.S. Department of Defense (PR101053, LC110202, and BC132124), the Mr. William H. Goodwin and Alice Goodwin, and the Commonwealth Foundation for Cancer Research and the Experimental Therapeutics Center.

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Address for reprints: Prasad S. Adusumilli, MD, FACS, FCCP, Deputy Chief and Associate Attending, Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (E-mail: adusumip@mskcc.org).

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With implementation of the new classification system for lung adenocarcinomas (ADC) by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society, tumors that were previously classified as either well or poorly differentiated are now classified on the basis of their histologic patterns: adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic, acinar, papillary, micropapillary, and solid.^{1,2} Of these patterns, the micropapillary-predominant pattern is a high-grade histologic subtype with poor prognosis. Our group was the first to demonstrate that the presence of micropapillary pattern ($\geq 5\%$) is independently associated with risk of local recurrence in patients treated with limited resection (ie, wedge resection) for small (≤ 2 cm) lung ADC.³ Risk of recurrence was higher when the surgical margin was < 1 cm but not when the surgical margin was ≥ 1 cm. Frequency of locoregional recurrence despite negative tumor margins prompted us to investigate the pathologic slides. We identified clusters of viable tumor cells at a distance from the tumor margin, within alveolar spaces, that were influencing frequency and location of recurrences and the prognosis. We coined the term “spread through alveolar spaces (STAS),” which we defined as the spread of tumor cells into air spaces in the lung parenchyma adjacent to the main tumor.⁴ Other investigators reproduced these results and showed that micropapillary-predominant ADC is associated with the highest rates of STAS and with the worst related overall and disease-free survivals.⁵

In this issue of *The Journal*, Morimoto and colleagues⁶ demonstrate the coexistence of free tumor clusters (FTCs), which they define as groups of > 3 clusters containing < 20 nonintegrated micropapillary tumor cells, within the air spaces, < 3 mm from the main tumor, in patients with micropapillary-positive tumors ($> 5\%$). Free tumor clusters

Prasad S. Adusumilli, MD, FACS, FCCP

Central Message

Clusters of viable tumor cells identified at a distance from the tumor margin, within alveolar spaces, can negatively influence recurrence and prognosis in lung adenocarcinomas.

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were associated with poor recurrence-free and overall survivals, and with higher rates of locoregional recurrence. Morimoto and colleagues⁶ measured the distance from the FTCs to the main tumor, and the distance did not exceed the diameter of the main tumor. They propose that the coexistence of FTCs should be considered a factor to upgrade the pathologically defined T stage.

This study adds to the recent literature investigating the reasons for the higher rates of locoregional recurrence after curative-intent resection for lung ADC. The strengths of this study are its focus on micropapillary-positive lung ADC; its careful approach, to include 3 clusters as an essential minimum to define FTCs, avoids misinterpretation of any artifacts; and the choice to measure the distance between FTCs and the main tumor, which is of practical significance in determining the appropriate resection for small lung ADC. The limitations of this study include the small cohort of patients with multiple pathological stages and shorter follow-up periods, and the inclusion of patients who received adjuvant therapy, which may have influenced outcomes. More importantly, the suggestion of Morimoto and colleagues⁶ on the basis of a very small number of patients, that the presence of FTCs should lead to upgrading the T stage is speculative yet provocative and necessitates further investigation in a larger cohort.

Free tumor clusters, a component of STAS in lung ADCs, hold significant prognostic implications. Investigations

focusing on the biologic mechanisms of STAS, as well as on the accurate identification of STAS in the resected specimen—or, even better, preoperatively—will change management of early-stage lung ADC.

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