Commentary: Preoperative identification of spread through air spaces (STAS): An elusive biomarker

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Patients with clinical T1a non–small cell lung cancer who underwent curative intent R0 resection had a disease-free survival of 63 to 65%. In patients with early-stage lung adenocarcinoma (ADC), high locoregional has been a perplexing issue, even when resected with negative margins. We and others have reported that micropapillary and solid histologic subtypes are associated with greater recurrence, specifically high locoregional recurrence following limited resection. Further investigations have identified tumor cells in the normal lung beyond tumor margin and coined them as “spread through air spaces” (STAS). Although some investigators have postulated that STAS is an artifact, STAS has shown to be a negative prognostic factor in patients with pulmonary malignancies, particularly in those with early-stage lung ADC. Furthermore, STAS has been associated with locoregional and distant recurrence, lymph node metastasis, and reduced survival.

To identify STAS before resection and use it as a marker to guide surgical decision-making, several groups have studied preoperative risk factors associated with STAS as well as the reliability of frozen section to identify STAS intraoperatively. Clinical risk factors associated with STAS have included the male sex, smoking history, higher carcinoembryonic antigen, and increased maximum standardized uptake value. Preoperative radiologic features, such as a tumor size of >2 cm and increased solid component, have been associated with STAS-positive tumors. Intraoperative assessment of STAS by frozen section has had low sensitivities of 44 to 71%. There is an unmet need of preoperatively identifying biomarkers that are predictive of STAS in patients with lung ADC.

In a retrospective cohort of 439 patients with clinical stage I-II non–small cell lung cancer, Tasnim and colleagues evaluated potential preoperative predictors of STAS. The strengths of their study include using a large patient population and analyzing clinical, radiographic, and molecular variables. Consistent with previous literature, the authors reported that preoperative imaging that shows solid, >2-cm tumors is a risk factor for STAS. An increased risk of STAS has also been reported in tumors with the presence of KRAS mutation on preoperative biopsy, >2.5 maximum standardized uptake value, and in patients aged <50 years. The study was limited by the number of patients who were reported to have undergone preoperative biopsy and molecular testing, a relatively short follow-up period (median overall survival, 2.3 years; median freedom from...
recurrence, 1.5 years), and a lack of histologic subtype analysis on preoperative biopsy.

As STAS is an indicator of tumor aggressiveness and associated with recurrence and reduced survival, there is an unmet need to identify biomarkers that are predictive of STAS. Additional investigation into the biology and molecular profile of STAS may provide insight into potential targets for adjuvant therapy or, if identified preoperatively, adjuncts to neoadjuvant therapy.

**Conflict of Interest Statement**

The authors reported no conflicts of interest.

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**References**


