STAS OR NOT STAS
SPREAD THROUGH AIR SPACES IS A FORM OF TUMOUR DISSEMINATION

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Spread through air spaces (STAS) is defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor.[1-3]
The distinction of STAS from artifacts can be challenging. This problem was addressed in the original diagnostic criteria for STAS.[1] Tumor cell artifacts need to be distinguished from STAS. Artifacts are more likely with the following morphology:[1]
1) randomly situated and ragged-edged clusters of tumor cells often at the edge of the tissue section or out of the plane of section of the tissue
2) lack of continuous spread in air spaces from the tumor edge to the most distant air space tumor cells;
3) the presence of jagged edges of tumor cell clusters
4) normal benign pneumocytes or bronchial cells with benign cytologic features or presence of cilia
5) linear strips of cells that are lifted off alveolar walls

A reproducibility study of 10 observers in 30 cases of powerpoint images testing the distinction between STAS and artifacts showed kappa values averaging 0.857 (range 0.624-1.00) which is almost perfect.[4] A follow-up study with scanned whole slides demonstrated similar results. In addition, many of the published studies that show the clinical significance of STAS specifically refer to these criteria. These findings provide evidence supporting the reproducibility of the proposed criteria to distinguish STAS from artifacts. Furthermore, application of these criteria in multiple studies has shown that STAS is a clinically relevant morphologic finding with prognostic importance.
STAS can manifest with three morphological patterns: micropapillary structures, solid nests of tumor cells, and single cells. [1] The importance and clinical significance of recognition of STAS is reflected by the many clinical studies demonstrating that it is a significant adverse prognostic factor. While most studies have been in lung adenocarcinoma the clinical significance of STAS has been demonstrated in all major histologic types of lung cancer studied including squamous cell carcinoma, pleomorphic carcinoma, small cell carcinoma, large cell neuroendocrine carcinoma and atypical carcinoid.1, [5-7]
Patients undergoing limited resection for their lung cancer appear to have a higher risk of recurrence than those having lobectomy.[1, 8-10]

A 3-dimensional reconstruction, immunohistochemical and multiplex immunofluorescence study showed that STAS tumor cells can be found attached to alveolar walls rather than free floating in air spaces as seen in two dimensions. [11] This suggests that tumor cells can 1) detach from the main tumor, 2) migrate through air spaces and 3) reattach to alveolar walls distant to the main tumor by vessel co-option, allowing the tumor cells to survive and grow.[11]

A recent study demonstrated that grossing specimen handling procedures to not impact the occurrence of STAS in lung cancer indicating that STAS is not a pathologist-related artifactual event caused by knife transportation of tumor cells during gross specimen handling.[12,13]

In addition, the identification of occult STAS tumor cells in lung tissue of the remaining unresected lobe after a limited resection where these second specimens were processed in pathology at a different time with different knives, provides evidence that STAS is an in vivo phenomenon and not an ex vivo artifact. Both of these studies support the concept that STAS is a form of tumor dissemination and not an artifact.

Recognition of STAS on frozen sections is challenging and while it may be possible, more study is needed.5 While expert thoracic pathologists may be able to recognize STAS on frozen section, it is premature for thoracic surgeons to expect their pathologists to provide this information in an intraoperative setting. In conclusion, STAS is regarded as a manifestation of tumor spread. While artifacts are an important differential diagnosis, reproducible criteria have been defined that allow for reliable distinction between STAS and artifacts. It is not recommended to include STAS cells into the percentages summed for lung adenocarcinoma subtypes or in determining the size T-descriptor for staging. It may play a role in the R-factor staging, but this remains to be determined.

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