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RE: Spread Through Air Spaces (STAS) is Prognostic in Atypical Carcinoid, Large Cell Neuroendocrine Carcinoma, and Small Cell Carcinoma of the Lung



To the Editor:

Since the concept of “spread through air spaces” (STAS) was included in the 2015 WHO book on classification of lung cancer, the manuscript by Aly et al.,¹ is the first study proposing detailed histologic criteria to distinguish STAS from other forms of “loose tumor fragments”: tumor floaters and artifacts¹ in lung neuroendocrine neoplasms. These expert opinion criteria are not supported by evidence showing prognostic differences in cases that exhibit STAS versus loose tumor fragments. In addition, the proposed criteria rely mostly on the detection of loose tumor fragments with smooth edges in spatial continuity with the tumor and within a certain distance to the lesion. Loose tumor fragments with jagged or ragged margins and/or those located far away from the tumor (“more than four airspaces

away,” as shown in Fig. 2) or at the edge of a tissue section are designated as an artifact.² The proposed criteria depend on an arbitrary distance between the tumor and the loose fragments, and the ability of pathologists to distinguish smooth from jagged or ragged edges. The difficulty of interpreting the characteristics of tumor borders is underscored by looking at the examples of STAS provided in Figure 1, taken at $\times 100$. In our opinion, it is difficult at this magnification to evaluate whether the fragments have round or jagged/ragged edges. The proposed criteria also raise questions as to why a tumor would always spread only through fragments with smooth borders. Indeed, previous studies have shown that the knife can disseminate tumor fragments with smooth or ragged margins radially from tumor edges into holes in tissue or into the edge of tissue sections.

A previous study of the presence of STAS on frozen section did not find sufficient evidence to support the routine reporting of STAS during intraoperative consultations.² To our knowledge, there are no clinical trials supporting the use of STAS as a predictive feature. Previous studies have used variable definitions for the identification of STAS on tissue sections, precluding the use of meta-analysis to aggregate available evidence about the association between STAS and prognosis.² Moreover, in the article by Aly et al.,¹ at least 88% (≥ 43 out of 49) of the STAS in typical carcinoids is present in cases without recurrence or lung cancer-specific death. Recent reports^{3,4} (and references herein) have described as artifacts the presence of loose fragments in different neoplastic and non-neoplastic lesions such as in diffuse idiopathic pulmonary neuroendocrine cell hyperplasia.⁴ Studies performing

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3D reconstructions evaluating the continuity between the main tumor and the detached cells have shown that the latter represent tentacles of inherently fragile structures.⁵

In summary, the diagnostic criteria for the distinction between STAS and artifacts proposed by Aly et al.,¹ need to be defined in more detail with studies showing diagnostic reproducibility and correlation with prognosis and prediction before the controversy as to whether pathologists can distinguish the so-called STAS from artifacts is put to rest.

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