THE RELEVANCE OF STAS FOR THE THORACIC SURGEON

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Tumour spread through air spaces(STAS) is defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumour [1]. For pathologists it remains a controversial topic as it should be distinguished from findings suggesting artefactual spread of tumor cells.

In a series of 261 patients who underwent resection of a stage I-II lung adenocarcinoma 3D reconstruction of histological slices was performed to detect specific tumor islands, defined as tumor cells isolated within alveolar spaces [2]. There were 203 patients without tumor islands and 58 with tumor islands. Those without tumor islands were most commonly associated with minimally invasive adenocarcinoma, lepidic growth and EGFR mutations. Those with tumor islands were mainly smokers with tumors showing a higher nuclear grade, micropapillary or solid patterns, and KRAS mutations. Five-year recurrence-free survival without tumor islands was 74.4% in contrast to 44.6% for those with tumor islands (p= 0.01). This remained significant in multivariate analysis. In patients with tumor islands representing STAS, more intensive surveillance and/or further intervention are indicated [2].

Prognostic impact of intra-alveolar tumor spread was evaluated in 569 resected pulmonary adenocarcinomas [3]. Limited STAS was detected in 21.6%, and extensive STAS in 29.0%. STAS was more prevalent in higher stage tumors and those with positive nodes, and demonstrated a lower rate of EGFR mutations but a higher rate of BRAF mutations. STAS was associated with a reduced overall and disease-free survival rate. The authors concluded that STAS is a morphologic prognostic factor that should be implemented in routine diagnostic evaluation and reporting [3].

Regarding the extent of surgical resection and risk of recurrence, STAS was studied in 411 patients who underwent resection of a stage I lung adenocarcinoma between 1995 and 2006 [4]. Limited resection was performed in 120 patients and lobectomy in 291 patients. Considering the patients with limited resection, the risk of any recurrence with STAS was 42.6% in contrast to 10.9% in those without STAS ($p < .001$). STAS was associated with a higher risk of local and distant recurrences. In the patients who had undergone lobectomy, STAS was not associated with any recurrence. In multivariate analysis STAS was independently associated with risk of developing recurrence (HR 3.08, p=.014). The authors conclude that STAS is a significant risk factor of recurrence in patients with small lung adenocarcinomas treated with limited resection [4].

A similar study question was addressed in 909 patients undergoing resection for small lung adenocarcinomas until 2 cm [5]. A total of 557 patients underwent lobectomy, and 352 patients sublobar resection. In this study, also an external validation was performed in 708 patients. After lobectomy, risk factors for recurrence were micropapillary and solid patterns, lymphovascular invasion and necrosis. For sublobar resection, micropapillary pattern, STAS, lymphovascular invasion and necrosis were important risk factors. Both internal and external validation showed good discrimination [5].

Is STAS also a prognostic factor in neuroendocrine tumors? This specific question was raised in a series of 487 patients who underwent resection of a pathological stage I-III lung neuroendocrine tumor (NET) between 1992 and 2012 [6]. There were 299 typical carcinoids (TC), 38 atypical carcinoids (AC), 93 large cell neuroendocrine carcinomas (LCNEC) and 57 small cell lung cancers (SCLC). STAS was present in 26% of NET (16% TC, 37% AC, 43% LCNEC, 46% SCLC). In AC, LCNEC and SCLC, STAS was associated with distant metastasis, a higher cumulative incidence of recurrence (CIR) and a higher lung cancer-specific cumulative incidence of death (LC-CID). For TC the mortality and recurrence rates were too low for prognostic evaluation. On multivariable analysis, STAS remained significant for CIR with a HR=2.85, and also for LC-CID with a HR = 2.72. So, for AC, LCNEC and SCLC, STAS is an independent poor prognostic factor.

So, from these clinical studies it is clear that not only pathologists but also thoracic surgeons should be aware of the existence of STAS. In case a limited or sublobar resection was performed, a completion lobectomy has to be considered when STAS is demonstrated on final pathological examination in order to decrease the recurrence risk. However, specific treatment strategies including chemotherapy and/or immunotherapy still have to be developed [7-8].

References

1. WHO classification of Tumours - 5th Edition. Thoracic Tumours. International Agency for Research on Cancer (IARC). Lyon, France 2021 pp.71-72. ISBN 9789283245063
2. Onozato ML. Am J Surg Pathol 2013; 37:287-94
3. Warth A. Am J Surg Pathol 2015; 39:793-801
4. Kadota K. J Thorac Oncol 2015; 10:806-14
5. Bains S. J Thorac Oncol 2019; 14:72-86
6. Aly R. J Thorac Oncol 2019; 14:1583-93
7. Jia M. Cancer Manag Res 2020; 12:2743-52
8. Shih A. Histopathology 2020; 77:173-180