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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Impacts of thoracoscopic surgery and high grade histologic subtypes on spread through air spaces in small stage I lung adenocarcinomas

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Abstract

Objectives Spread through air spaces (STAS) as a pattern of invasion in lung adenocarcinomas had been recognized by WHO in 2015. Moreover, STAS was associated significantly with aggressive micropapillary or solid components when presented predominant pattern in lung adenocarcinomas, which had a poor prognostic significance. Small amounts of micropapillary or solid with components could also reduce overall survival and recurrence-free survival but its impact on STAS is unknown now. Some studies have demonstrated manipulations of surgeons and pathologists could affect STAS but the degree of these impacts is not clear.

Materials and methods We reviewed resected small (≤2 cm) stage I invasive lung adenocarcinomas by thoracoscopic surgery at our institution from January 2017 to October 2018 ($n=277$). Micropapillary or solid pattern was considered to be present when the subtype occupied at least 1% of the entire tumor. Lobectomy and segmentectomy were performed using three portals thoracoscopic surgery. Statistical analysis was performed to analyze the correlations of STAS and clinicopathological characteristics. Moreover, we also analyzed the correlated factors of STAS in solid nodules.

Results STAS was found in 59 of 163 (36.2%) lobectomy cases and 27 of 114 (23.7%) limited resection cases. Lobectomy group showed a higher incidence of STAS compared with limited resection group ($p=0.027$), but the difference was disappeared in multivariate analysis, which showed that STAS was significantly correlated to solid nodules and presence of high grade histologic subtype (mircopapillary or solid). However, both lobectomy and presence of high grade histologic subtype were significantly correlated with STAS in solid nodules.

Conclusions The small amounts of high grade histologic subtypes were also associated with STAS. Thoracoscopic surgery could affect STAS to some degree.

Keywords Lung adenocarcinoma · Tumor spread through air spaces · Lung cancer surgery

Introduction

The concept of spread through air spaces (STAS) was proposed recently and included in the 2015 World Health Organization (WHO) classification for lung cancer as a pattern of invasion, which was defined as "micropapillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces" (Travis et al. 2015). Most of studies showed that the STAS was a significant prognostic factor of poor overall survival (OS) and recurrence-free survival (RFS) in early lung adenocarcinomas (Onozato et al. 2013; Toyokawa et al. 2018; Dai et al. 2017). Even it had been regarded as an indicator for lobectomy rather than sublobar resection (Kadota et al. 2015; Shiono et al. 2018). Subsequently, its value as a unfavorable prognostic factor was also investigated in advanced adenocarcinoma and lung squamous cell carcinoma (Warth et al. 2015; Lu et al. 2017). Aggressive micropapillary or solid components are associated significantly with STAS when they represent the predominant pattern (Onozato et al. 2013; Dai et al. 2017). Small amounts of micropapillary or solid components (≥1% components) have been demonstrated

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to reduce poor patient outcomes also (Cha et al. 2014), but its correlation with STAS is unknown. In this study, we investigated the percentage of micropapillary or solid pattern which could impact presence of STAS. Moreover, besides biological factor, physical factor such as squeezing pressure-induced tumor cell detachment is another major factor which might affect the presence of STAS. During the process of thoracoscopic surgery, pulling lung specimen out through the small incision is the most possible step to produce such kind of squeezing pressure. It is well known that lung has loosen structure due to presence of air spaces, and the bigger the specimen size is, the larger the squeezing pressure can be produced when sample is pulled out through a small incision in thoracoscopic surgery. In our department, the size of utility incision in video-assisted thoracoscopic surgery (VATS) which was also used for pulling out the sample was about 3 cm. We, therefore, hypothesized that bigger specimen in lobectomy was more likely to present STAS than smaller specimen in sublobar resection. Hence, the impact of thoracoscopic surgery on STAS was also be investigated in this study.

Materials and methods

Patient cohorts

The study was approved by our institutional review board and informed consent was waived because of retrospective study. Pathologic stage determination was based on the AJCC 8th edition staging (American Joint Committee on Cancer 2017). We reviewed patients with primary lung adenocarcinoma that had been surgically resected by VATS including both lobectomy and limited resection (wedge resection or segmentectomy) and diagnosed as small (≤ 2 cm), pathological stage I disease from January 2017 to October 2018. Cases with neoadjuvant therapy, multiple nodules, positive surgical margin, interim thoracotomy before removing lung tissue, biopsy or location before surgery, other histological components (such as squamous, variants of invasive adenocarcinoma, neuroendocrine differentiation), and no available tumor slides for review were excluded from the study cohort. Patients who received middle lobe resection and combined segmentectomy (≥ 2 adjacent segments) were also excluded, but the resection of two adjacent subsegments was involved. According to these criteria, we enrolled a total of 277 patients. Tissue specimens were retrieved from the registry of the department of pathology in our medical center. Clinical and demographic information was obtained from the medical record.

Preoperative examination and surgical procedures

All of the participating patients underwent lung high-resolution computer tomography (CT) scans with a thickness of 1 mm to identify tumor location and excision extension. Additional diagnostic examinations [including head magnetic resonance imaging (MRI) or CT, upper abdominal contrast-enhanced CT, bone scan, pulmonary function analysis, bronchoscopy] were performed before surgery, and none of lesions were found above the lung segment bronchus. Images of nodules on CT were divided into solid or non-solid nodules. Tree portals VATS was performed in our department. The Thoracoport in the 7th intercostal space at the mid-axillary line and an assistant incision (2 cm) in the 9th intercostal space (between the posterior axillary line and subscapular line) were needed. Specimens were taken out from utility portal, which was a about 3 cm incision in the 3th or 4th intercostal space at mid-axillary line. Lobectomy was performed routinely according to single-direction procedure unless it was difficult. This manner can reduce frequent turn-over of the lung lobes (Liu et al. 2010). We avoid clamping the tumor directly when wedge resection and segmentectomy. Intersegmental plane was identify in the segmentectomy by inflation-deflation manner (Oizumi et al. 2014), and the inflated lung tissue around tumor could play the role of elastic cushion to reduce the impact of mechanical forces on the tumor. The specimen bag was used to prevent tumor from breaking or dissemination. Systematic mediastinal lymph node dissection or sampling (≥ 3 of mediastinal lymph node stations including subcrinal station and a total resected lymph nodes number > 6) was also performed.

Pathological examination

In our institution, a series of standard operating procedures in specimen processing were established in 2016 for reducing confounding factors. All specimens were transported to pathology department for formalin-fixed before prosection as soon as possible, and processes of prosection and sampling were uniform. It was demanded to clean the knife blade after each slice using wet gauze. The hematoxylin and eosin (HE)—stained slides of resected tumor specimens were reviewed by two pathologists, respectively (LL Jiang and WY Wang), who were blinded to the clinical characteristics of patients.

Because the category according to distance between detached tumor cells and the main tumor had no significance with respect to survival times, we adopted the definition of STAS proposed by Kadota and WHO (Travis et al. 2015; Kadota et al. 2015). STAS was distinguished

from artificially detached tumor cells during specimen processing and clustered alveolar macrophages through morphology and immunohistochemistry. Tumor cells were not scored as STAS unless there was no direct connection of the cells to the main tumor, STAS was also excluded if tumor cell clusters had jagged edges, which was caused by knife cut during specimen processing. Sometimes, immunohistochemistry was needed to distinguish tumor cells from clustered macrophages through immunostain for cytokeratin 7 and CD163.

The adenocarcinoma was classified using the 2015 WHO classification criteria and histologic subtype was assessed according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) histological classification, in which lepidic pattern was regarded as a noninvasive component and had a favorable prognosis, but aggressive solid or micropapillary pattern had a poor prognostic significance (Travis et al. 2011, 2015). In this article, we adopted a three-tiered grading scheme for histologic subtypes of invasive adenocarcinoma, in which lepidic adenocarcinoma was low grade, acinar and papillary tumors were intermediate grade; solid and micropapillary tumors were high grade. The percentage of each histologic subtype (lepidic, acinar, papillary, solid, and micropapillary) was recorded in 5% increments and tumors were classified on the basis of predominant pattern. For solid and micropapillary patterns, small amounts of micropapillary or solid component were also considered to be present if the percentage reached 1% of the overall tumor (Figs. 1 and 2). Presence of visceral pleural invasion, lymphovascular invasion was also recorded. In the event of disagreement, discussion between two pathologists was necessary before reaching a consensus.

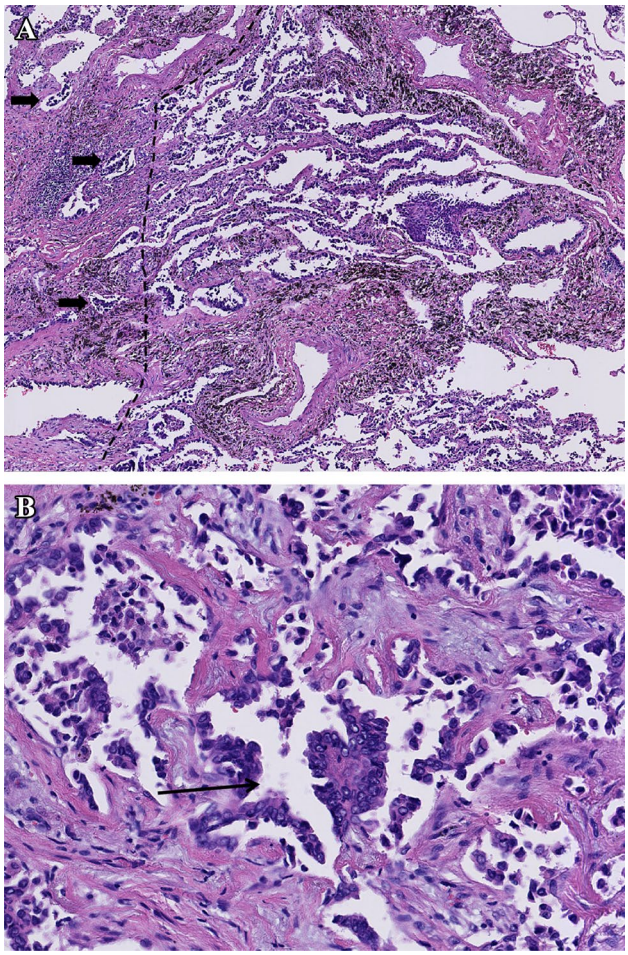

Fig. 1 **a** Small amount micropapillary components (about 3%) in papillary-predominant adenocarcinoma exhibiting STAS (short arrows) (×50). **b** Micropapillary pattern (long arrow) (×200)

Statistical analysis

Demographic and clinicopathologic data are presented as median (range) for continuous variables and number (percentage) for categorical data. Categorical variables were compared by Pearson's χ^2 test and continuity correction. Since age, tumour size and utility portal size were non-parametric variables, numerical variables were compared by Wilcoxon rank-sum test. To adjust potential confounders of the association between clinicopathologic characteristics and STAS, variables that achieved statistical significance in the univariate analysis were included in the multivariate analysis using the logistic regression model. Similarly, we also analyzed the correlated factors of STAS in solid nodules separately. In this study, all p values were based on two-sided statistical analysis and considered to be statistically significant at < 0.05. Analyses were performed with SPSS 22.0 software (IBM Corporation, Armonk, NY, USA).

Results

Patient demographics and clinicopathologic characteristics

The median age of the patients at the time of surgery was 55 (range 24–80) years. Of the 277 patients, 110 (39.7%) were male and 167 (60.3%) were female. STAS was observed in 86 cases (31.0%). The level of serum carcinoembryonic antigen (CEA) was higher in 40 cases (14.4%). There were 208 (75.1%) non-smokers, 69 (24.9%) past smokers or current smokers among the patients. The median tumor size was 1.5 (range 0.5–2.0) cm, and utility portal size was 3.4 (range 3.0–4.1) cm. The number of patients with lymphovascular invasion was 17 (6.1%) and 40 (14.4%) patients were observed with visceral pleural invasion. There were 75 patients with predominant lepidic pattern, 40 with predominant papillary pattern, 155 with predominant acinar pattern, 7 with predominant solid pattern and no predominant micropapillary pattern

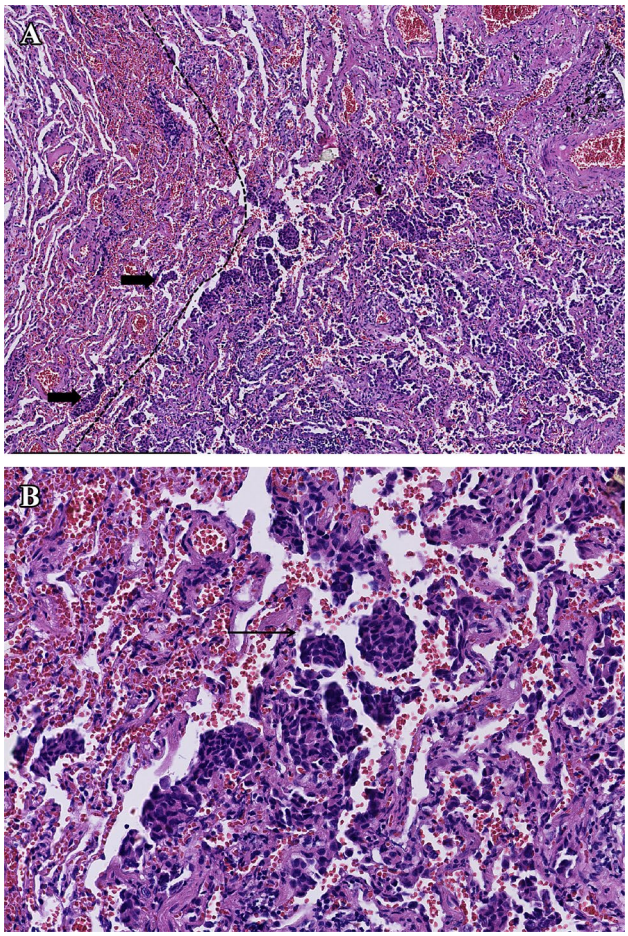

Fig. 2 **a** Small amount solid components (about 2%) in papillary-predominant adenocarcinoma exhibiting STAS (short arrows) (×50). **b** Solid pattern (long arrow) (×200)

in our study. Majority of patients [253 of 277 (91.3%) patients] contained intermediate grade histologic subtypes. Lepidic pattern presented in 173 (62.5%) patients and 62 (22.4%) patients included high grade histologic subtypes.

These features of gender, age, smoking condition, tumor location, histologic subtype, image, visceral pleural invasion, lymphovascular invasion, utility portal size, and tumor size were analyzed between lobectomy group and limited resection group. Only the tumor size which was 1.4 (1.1–1.7) cm in limited resection group and 1.5 (1.3–1.7) cm in lobectomy group was significant difference ($p = 0.042$). The incidence of STAS in lobectomy group [59 of 165 (35.8%) patients] was higher than limited resection group [27 of 112 (24.1%) patients] ($p = 0.027$).

Association between STAS and clinicopathological features

Clinicopathological features of patients according to STAS are presented in Table 1. In STAS positive group, the proportion of patients who received lobectomy by VATS, and who had a solid nodule on chest CT, high grade histologic subtypes, lymphovascular and pleural invasion was significantly higher compared with STAS negative group. In the multivariate analysis, positive STAS was significantly related to solid nodule on CT ($p < 0.001$), and presence of high grade histologic subtypes ($p < 0.001$) (Table 2).

Association between STAS and clinicopathological features in solid nodules

To further clarify the impact of thoracoscopic surgery, we analyzed the correlated factors of STAS in solid nodules. Clinicopathological features of patients are presented in Table 3. Presence of high grade histologic subtypes ($p = 0.004$) and lobectomy ($p = 0.046$) were significantly associated with positive STAS in the logistic regression model with covariates consisting of surgery procedure, presence of high grade histologic subtypes, visceral pleural invasion, and tumor size (Table 4).

Discussion

The concept of STAS is evolved from the phenomenon of 'loose tumor fragments in the lung', which has been regarded as an artifact. Researchers began to pay attention on this phenomenon from Onozato's study which demonstrated 'tumor islands' might be a prognostic factor in resected early stage lung adenocarcinomas (Onozato et al. 2013). More studies were performed subsequently, most of which focused on early stage or small size lung cancer. STAS was demonstrated as an independent prognostic factor for higher recurrence and decreased survival in pathological stage I adenocarcinoma, which was regarded as an indicator to choose appropriate surgical procedure and further treatment decisions (Warth et al. 2015; Shiono and Yanagawa 2016). However, the tumor infiltration pattern of STAS is not clear now, a underlying biological explanation for the association of STAS with poor prognosis is that displacement of tumor cells is simply seen in poorly differentiated, highly discohesive tumors. According to IASLC/ATS/ERS histological classification, the percentage of each histologic subtype was assessed semi-quantitatively in 5% increments and tumors were classified based on predominant subtype. STAS associated significantly with aggressive micropapillary or solid component when presented in predominant pattern. However, studies had demonstrated that small amounts of micropapillary or solid components could also reduce DFS and OS. The relation between small amounts of micropapillary or solid components and STAS was not clear. In this study, there was no predominant micropapillary pattern and only seven patients were observed with

Table 1 Associations between clinicopathological features and STAS

Characteristics	STAS(+) ($n = 86$)	STAS(−) ($n = 191$)	p
Median age (years), IQR	57 (50–65)	54 (49–62)	0.082
Gender			0.760
Male	33	77	
Female	53	114	
Smoking			0.439
Never	62	146	
Former/current	24	45	
Tumor location			0.109
Upper	50	130	
Lower	36	61	
Utility incision size (cm), IQR	3.5 (3.3–3.8)	3.4 (3.2–3.8)	0.542
Surgery			0.027
Lobectomy	59	104	
Limited resection	27	87	
Median tumor size (cm), IQR	1.6 (1.3–1.8)	1.4 (1.2–1.7)	0.001
Low grade histologic subtyp[a]			< 0.001
Absent	54	50	
Present	32	141	
Intermediate grade histologic subtype[b]			0.040
Absent	3	21	
Present	83	170	
High grade histologic subtype[c]			< 0.001
Absent	36	179	
Present	50	12	
Visceral pleural invasion			< 0.001
Absent	63	174	
Present	23	17	
Lymphovascular invasion			0.011
Absent	76	184	
Present	10	7	
Nodules on CT			< 0.001
Non-solid	24	139	
Solid	62	52	
Carcinoembryonic antigen			0.559
Normal	72	165	
High	14	26	

IQR interquartile range, *STAS* spread through air spaces, *CT* computed tomography

[a]Lepidic; [b]acinar and papillary; [c]solid and micropapillary

predominant solid pattern. In patients with high grade histologic subtypes, 64.5% patients [40 of 62] exceeded 5% increments and 80.6% patients [50 of 62] appeared STAS, which accounted for 58.1% [50 of 86] of all positive STAS. In our study, multivariate analysis demonstrated that presence of high grade histologic subtypes was an independent predictive factor of STAS, which was not mentioned before. When the seven patients with predominant solid pattern were excluded, STAS was also significantly correlated with the presence of high grade histologic subtypes (OR 6.643, 95% CI 3.095–14.256, $p < 0.001$), visceral pleural invasion (OR 2.377, 95% CI 1.037–5.446, $p = 0.041$) and solid nodule on CT (OR 4.497, 95% CI 2.384–8.482, $p < 0.001$). So, the impact of relatively small amounts of micropapillary or solid components might be ignored. Furthermore, if the effect of STAS as a prognostic factor was related to the amount of high grade histologic subtypes, it was easy to explain the association between increasing STAS and shorter RFS (Uruga et al. 2017; Zombori et al. 2018). In addition, STAS was mainly presented with micropapillary cluster which was compatible with the cytoarchitectural features of the micropapillary pattern (Kadota et al. 2015). Taken

Table 2 Multivariate analysis of the correlation between clinicopathological features and STAS

Variables	Odds ratio (95% CI)	*p*
Solid nodule on CT	3.547 (1.763–7.136)	< 0.001
Presence of high grade histologic subtype[a]	6.037 (2.666–13.671)	< 0.001
Presence of intermediate grade histologic subtype[b]	2.558 (0.581–11.534)	0.212
Presence of low grade histologic subtype[c]	0.713 (0.353–1.438)	0.345
Visceral pleural invasion	2.019 (0.845–4.823)	0.114
Lobectomy	0.986 (0.486–2.001)	0.970
Tumor size	1.843 (0.657–5.167)	0.245
Lymphovascular invasion	1.362 (0.420–4.417)	0.607

CI confidence interval

[a]Lepidic ; [b]acinar and papillary; [c]solid and micropapillary

Table 3 Associations between clinicopathologic features and STAS in solid nodules

Characteristics	STAS(+) ($n = 62$)	STAS(−) ($n = 52$)	*p*
Median age (years), IQR	56 (49–63)	58 (51–65)	0.934
Gender			0.867
Male	26	21	
Female	36	31	
Smoking			0.472
Never	44	40	
Former/current	18	12	
Tumor location			0.551
Upper	38	29	
Lower	24	23	
Utility incision size (cm), IQR	3.5 (3.3–3.7)	3.5 (3.3–3.6)	0.784
Surgery			0.039
Lobectomy	46	29	
Limited resection	16	23	
Median tumor size (cm), IQR	1.5 (1.4–1.7)	1.4 (1.2–1.7)	0.031
Low grade histologic subtyp[a]			0.063
Absent	46	30	
Present	16	22	
Intermediate grade histologic subtype[b]			0.842*
Absent	4	2	
Present	58	50	
High grade histologic subtype[c]			< 0.001
Absent	26	42	
Present	36	10	
Visceral pleural invasion			0.035
Absent	45	46	
Present	17	6	
Lymphovascular			0.480[d]
Absent	55	49	
Present	7	3	
Carcinoembryonic antigen			0.779
Normal	50	43	
High	12	9	

IQR interquartile range, *STAS* spread through air spaces, *CT* computed tomography

[a]Lepidic; [b]acinar and papillary; [c]solid and micropapillary; [d]continuity correction

Table 4 Multivariate analysis of the correlation between clinicopathological features and STAS in solid nodules

Variables	Odds ratio (95% CI)	*p*
Presence of high grade histologic subtype[a]	3.508 (1.487–8.275)	0.004
Visceral pleural invasion	1.406 (0.488–4.048)	0.528
Lobectomy	2.413 (1.015–5.735)	0.046
Tumor size	2.697 (0.678–10.732)	0.159

CI confidence interval

[a]Solid and micropapillary

together, further studies were essential to clarify the correlation between STAS and high grade histologic subtypes.

Furthermore, we all known it is usually a difficult and time-consuming process to remove lung specimen through tiny incision during thoracoscopic surgery, in which lung lobe including tumor always is squeezed seriously. In this article, we study the possible impact of lobectomy and limited resection by VATS on STAS in early stage lung adenocarcinomas. Prior to this article, some studies had compared the incidence of STAS by lobectomy versus segmentectomy or other surgical procedures. But some questions presented in these studies. For instance, thoracotomy and thoracoscopic surgery were not evaluated separately and the clinicopathological features between groups were not evaluated to ensure balanced enrollment, the criteria of systematic lymph node dissection and sampling were unknown, preoperative manipulations including needle biopsy or location and specific procedures in specimen processing were not described also. Even there was not a uniform definition of STAS. Moreover, some studies demonstrated that knife could cause tissue contaminant on a slide during specimen prosection and the number of loose tumor cells was higher in fresh specimens than unfixed tissues (Thunnissen et al. 2016; Blaauwgeers et al. 2017). So many confounding factors were not considered well and conclusions were not consistent as a result (Kadota et al. 2015; Uruga et al. 2017). Our medical center performed strict principles for specimen processing and surgery, which were all outlined in our methods.

In our study, the incidence of STAS is about 31%,which is similar to previous researches (Dai et al. 2017; Kadota et al. 2015). Lobectomy group had higher incidence of STAS than limited group ($p = 0.027$), but the difference was not significant in the multivariate analysis, which indicated positive STAS was significantly related to solid nodule on CT and presence of high grade histologic subtypes. Solid nodules might have higher proportion of invasive components and were easier to produce loose tumor cells after being squeezed. Subsequently, we analyzed the association between STAS and clinicopathological features in solid nodules and incorporated variables that had statistical significance in the univariate analysis into the multivariate analysis using the logistic regression model. We found lobectomy were significantly associated with positive STAS (odds ratio 2.413, 95% confidence interval 1.015–5.735, $p = 0.046$) in solid nodules. Interestingly, the tumor size was not significantly correlated with STAS, majority of tumors limited to larger size (> 1 cm) in this study might account for the result. So the impact of thoracoscopic surgery on STAS should be assessed in further studies.

Meanwhile, we need to pay attention on main comorbidities with lung cancer. Chronic obstructive pulmonary disease (COPD), tuberculosis, and idiopathic pulmonary fibrosis can change the texture of lung, which might be potential factors to affect STAS. Displaced tumor cells in other organs caused by biopsy procedures had been proved. Even the incidence and amount of tumor displacement were inversely related to the time interval between core biopsy and excision in breast samples (Diaz et al. 1999). The impact of biopsy or location before surgery also should be investigated.

This study has several limitations. First, it was retrospective in nature and conducted in a single center. Although standard procedures were performed in pulmonary resection and tissue handling, there were other confounding factors (e.g., surgeons used their hands and applied pressure to the lung tissue for locating small tumors within lung, tumor cells might be displaced by the knife along the plane of sectioning) could not be balanced (Blaauwgeers et al. 2017; Warth 2017). Second, present exclusion criteria of artifact are almost based on morphology and subjective, which can not give credible explanation for all controversial conclusions. Third, recurrence and survival outcomes were not presented in our research.

In summary, relatively low incidence, ignored impact of high grade histologic subtypes, confounding factors including surgical procedure and specimen handling and other mechanisms of ex vivo artifacts demanded us to review the value of STAS in small stage I lung adenocarcinomas as an invasive pattern carefully. It was necessary to consider these factors before expanding the research of STAS. More prospective studies are needed to develop a precise definition which can reduce and quantify confounding factors in the future. Certainly, amounts of work needs to be done at the molecular level, which can help us understand what make tumor cells prone to loss of cohesiveness and spread through air spaces. Otherwise, patients will worry whether tumor cells can spread by cough or turning over.

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Compliance with ethical standards

Conflict of interest The authors have stated that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The study was approved by our institutional review board and informed consent was waived because of retrospective study.

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