

## ORIGINAL ARTICLE

# Significance of spread through air spaces in early-stage lung adenocarcinomas undergoing limited resection

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Early-stage; limited resection; lung adenocarcinoma; spread through air spaces; surgical margin recurrence.

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**Abstract**

**Background:** In early-stage lung adenocarcinomas, spread through air spaces (STAS) are reported to be a prognostic factor in patients who have undergone sublobar resection, but not lobectomy. In contrast, reports have also shown that STAS is significantly associated with poor survival outcomes after lobectomy, but not after limited resection. Thus, the prognostic impact of STAS differs according to published reports.

**Methods:** A total of 82 patients with early-stage adenocarcinomas who underwent limited resection and whose STAS status could be examined were enrolled in this retrospective study. We evaluated the association between STAS and clinicopathological characteristics and postoperative survival.

**Results:** Among 82 patients, 31 (37.8%) were positive for STAS, while 51 (62.2%) were negative. STAS was significantly associated with advanced tumor stage ( $P < 0.01$ ), lower histological differentiation ( $P = 0.01$ ), and the presence of pleural invasion ( $P = 0.01$ ). Patients with STAS had significantly shorter recurrence-free survival (RFS) and overall survival (OS) than those without STAS ( $P < 0.01$  and  $P = 0.02$ , respectively). According to multivariate analysis, positivity for STAS was an independent prognostic parameter for RFS ( $P < 0.01$ ), but not OS ( $P = 0.45$ ). Three patients who developed surgical margin recurrence and one patient who developed distant recurrence were all positive for STAS.

**Conclusions:** STAS was predictive of poor postoperative survival in patients with early-stage adenocarcinomas treated with limited resection and was associated with surgical margin recurrence.

**Introduction**

Lung cancer is the leading cause of cancer-related death worldwide, and its prognosis remains poor.<sup>1</sup> Although recent advances in molecular-targeted agents and immune checkpoint inhibitors have prolonged the survival of patients with lung cancer, surgical resection remains the most curable treatment option for patients with early-stage non-small cell lung cancer (NSCLC), and specifically, stage I NSCLC can be cured by lobar resection combined with nodal dissection.<sup>2</sup> Furthermore, a nonrandomized, confirmatory, phase III study conducted in Japan (JCOG0804/WJOG4507L) suggested that sublobar resection (mainly wedge resection) achieved local control and recurrence-free survival (RFS) for radiologically noninvasive lung cancer

with a maximum tumor diameter  $\leq 2$  cm and a solid tumor ratio  $\leq 0.25$ , as shown by thin-section computed tomography (CT).<sup>3</sup> Several studies are in progress to validate the use of sublobar resection for early-stage lung cancer stratified by CT findings and their results will elucidate whether limited resection for lung cancer is not only function-preserving but also curative surgery.<sup>4</sup> Thus, limited resection is one of the main focuses in the management of early-stage lung cancer.

Spread through air spaces (STAS) is a recently recognized invasive pattern of lung cancer, defined as “micro-papillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces.”<sup>5</sup> Although first introduced by Kadota *et al.* in 2015,<sup>6</sup> similar concepts,

including aerogenous spread with floating cancer cell clusters and tumor islands, have been reported.<sup>7–9</sup> Although the definite mechanisms of STAS have yet to be elucidated, several studies have shown an association with male gender, a history of smoking, and clinicopathologically invasive features, such as larger tumor diameter, the presence of pleural invasion, and histologically invasive types.<sup>6,10–12</sup>

Regarding the role of STAS as a significant prognostic factor, several reports have shown the negative impact of STAS on postoperative survival of resected NSCLC patients.<sup>6,11–16</sup> Particularly in early-stage lung adenocarcinomas, STAS is reported to be a prognostic factor in patients who have undergone limited resection, but not lobectomy.<sup>6</sup> A study also demonstrated that STAS was an independent prognostic factor of poor survival in patients with clinical stage IA lung cancer who underwent sublobar resection.<sup>17</sup> In contrast, another report showed that STAS was significantly associated with poor survival outcomes in patients who underwent lobectomy, but not in patients who underwent limited resection.<sup>12</sup> Thus, the prognostic impact of STAS in early-stage lung adenocarcinoma has yet to be definitively established.

In this translational study we investigated the prognostic significance of STAS in 82 patients with pathological stage I lung adenocarcinoma undergoing limited resection.

## Methods

### Patients

We retrospectively examined the data of patients who underwent surgical resection of primary lung adenocarcinoma between January 2003 and December 2012 at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University. Paraffin-embedded specimens were retrieved from the registry of the Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University. Among 276 patients with pathological stage I lung adenocarcinoma, 82 patients who were treated with limited resection and whose STAS status could be evaluated were enrolled. The clinicopathological features, including age at surgery, gender, smoking history, pathologic tumor node metastasis (TNM) stage (7th edition of the Lung Cancer Staging System), histological subtype (World Health Organization Classification 2015), and *EGFR* mutation status, were examined. *EGFR* status was determined in tumor tissues using the peptide nucleic acid-locked nucleic acid PCR clamp method (Mitsubishi Chemical Medience, Tokyo, Japan) in 54 specimens.<sup>18</sup> After surgery, routine checkups, including a physical examination, blood tests (including serum tumor markers), and

chest X-ray, were performed at three-month intervals for the first three years and at six-month intervals thereafter. CT was performed twice a year for the first three years and then at least annually thereafter. Clinical information and follow-up data were obtained from medical records. Local and distant recurrence were defined as previously described: locoregional recurrence was defined as disease recurrence at the surgical margin, ipsilateral hemithorax, or mediastinum; distant metastasis was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum.<sup>19</sup>

Our institutional review board approved the study.

### Spread through air spaces (STAS)

Spread through air spaces is defined as tumor cells within the air spaces in the lung parenchyma beyond the edge of the main tumor.<sup>11,20</sup> The pathologist ruled out single tumor cells/clusters with broken figures as artifacts because the finding suggests unnaturally separated cells/clusters. All tumors were evaluated at a magnification of  $\times 200$  using an optical microscope (BX40; Olympus, Tokyo, Japan).

### Statistical analysis

The associations between STAS and patient characteristics were analyzed using Fisher's exact test. Overall survival (OS) was defined as the duration from the initial surgery until death from any cause, while RFS was defined as the duration from the initial surgery until recurrence. Survival curves were generated using the Kaplan–Meier method and compared with the log-rank test. The prognostic factors for RFS and OS were assessed using a logistic regression model. All statistical analyses were conducted using JMP version 12 (SAS Institute, Cary, NC, USA). *P* values of  $< 0.05$  were considered to indicate statistically significant differences.

## Results

### Clinicopathological patient characteristics and their associations with STAS

Table 1 shows the characteristics of the patients included in this translational study. The median age of the patients was 71 years (range: 42–85) and 43 patients (52.4%) had a history of smoking. Surgical procedures included wedge resection (52, 63.4%) and segmentectomy (30, 36.6%). Twenty-nine (35.4%) and 46 (56.1%) patients underwent surgery for passive and curative intents, respectively. Pathological tumor stages were: 1a, 62 patients (75.6%); 1b, 10 (12.2%); and 2a, 10 (12.2%). STAS was observed in 31 patients (37.8%) and was significantly associated with

**Table 1** Patient characteristics

Factors	Number of patients (n = 82)
Age (years)	
Median	71
Range	42–85
Gender	
Female	42 (51.2%)
Male	40 (48.8%)
Smoking status	
Never-smoker	39 (47.6%)
Smoker	43 (52.4%)
CEA (ng/ml)†	
<3.2	55 (70.5%)
≥3.2	23 (29.5%)
Radiological tumor size (cm)	
≤2.0	67 (81.7%)
>2.0	15 (18.3%)
Consolidation/tumor ratio	
<0.25	29 (35.4%)
≥0.25	53 (64.6%)
Surgical procedure	
Wedge resection	52 (63.4%)
Segmentectomy	30 (36.6%)
Intent of surgical procedure	
Passive	29 (35.4%)
Curative	46 (56.1%)
Unknown	7 (8.5%)
Pathological tumor stage	
1a	62 (75.6%)
1b	10 (12.2%)
2a	10 (12.2%)
Histological differentiation	
Grade 1	59 (72.0%)
Grade 2	20 (24.4%)
Grade 3	3 (3.6%)
pl	
Negative	75 (91.5%)
Positive	7 (8.5%)
ly	
Negative	80 (97.6%)
Positive	2 (2.4%)
v	
Negative	75 (91.5%)
Positive	7 (8.5%)
Histological subtype	
AAH/AIS/MIA	27 (33.0%)
Lepidic predominant	9 (11.0%)
Papillary predominant	52 (63.4%)
Acinar predominant	1 (1.2%)
Micropapillary predominant	0 (0.0%)
Solid predominant	1 (1.2%)
Variants	1 (1.2%)
EGFR†	
Wildtype	30 (55.6%)
Mutant	24 (44.4%)
STAS	
Negative	51 (62.2%)
Positive	31 (37.8%)

†Cases in which data were available. AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; CEA, carcinoembryonic antigen; ly, lymphatic invasion; MIA, minimally invasive adenocarcinoma; pl, pleural invasion; STAS, spread through air spaces; v, vascular invasion.

advanced tumor stage ( $P < 0.01$ ), poorer histological differentiation ( $P = 0.01$ ), and the presence of pleural invasion ( $P = 0.04$ ) (Table 2).

### Survival analyses according to the presence of STAS

The median follow-up time after surgery was five years. Ten patients (12.2%) experienced recurrence and 10 patients (12.2%) died. Patients with STAS had significantly shorter RFS and OS than those without STAS ( $P < 0.04$  and  $P = 0.02$ , respectively) (Fig 1). The five-year RFS rates in patients with and without STAS were 69.2% and 96.7%, respectively. The five-year OS rates in patients with and without STAS were 79.2% and 92.7%, respectively.

### Univariate and multivariate analyses of survival according to STAS

Univariate analysis showed that carcinoembryonic antigen, histological differentiation, and STAS were significantly associated with RFS (Table 3). In multivariate analysis, these factors remained independent prognostic indicators of poor RFS (Table 3). Although STAS was significantly associated with poor OS in univariate analysis, multivariate analysis failed to demonstrate STAS as an independent prognostic factor of OS (Table S1).

### Recurrence pattern according to STAS

Among 82 patients, 10 (12.2%) experienced recurrence and a significant association was observed between recurrence and the presence of STAS ( $P < 0.01$ ) (Table 4). Locoregional recurrence was observed in nine (11.0%) patients and all but one were positive for STAS. Locoregional recurrence included surgical margin recurrence (3 patients), pulmonary metastasis (1 patient), lymph node metastasis (3 patients), and pleural dissemination (1 patient). Three patients (3.7%) who developed surgical margin recurrence were positive for STAS. One patient with STAS developed distant metastasis in the brain and bone.

### Discussion

The present study demonstrated that 31 (37.8%) out of 82 lung adenocarcinomas treated via limited resection were

**Table 2** The association between STAS and clinicopathological factors in lung adenocarcinoma patients who underwent limited resection

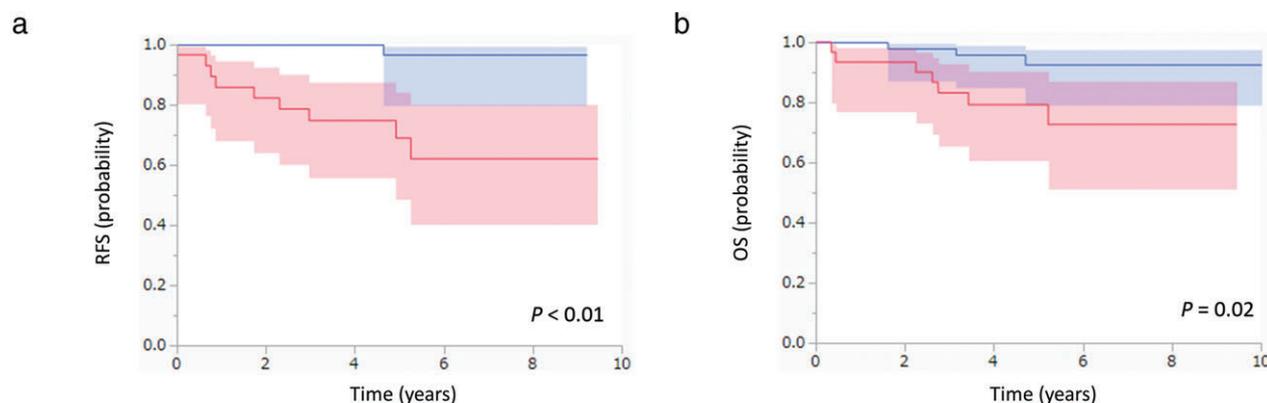
Factors	STAS (n = 82)		P
	Negative (n = 51)	Positive (n = 31)	
Age (years)			
< 70	18 (35.3%)	17 (54.8%)	0.11
≥ 70	33 (64.7%)	14 (45.2%)	
Gender			
Female	25 (49.0%)	17 (54.8%)	0.65
Male	26 (51.0%)	14 (45.2%)	
Smoking history			
Never-smoker	25 (49.0%)	14 (45.2%)	0.82
Smoker	26 (51.0%)	17 (54.8%)	
CEA (ng/ml)†			
<3.2	38 (77.6%)	17 (58.6%)	0.12
≥3.2	11 (22.4%)	12 (41.1%)	
Radiological tumor size (cm)			
≤ 2.0	43 (84.3%)	24 (77.4%)	0.56
> 2.0	8 (15.7%)	7 (22.6%)	
Consolidation/tumor ratio			
< 0.25	29 (41.2%)	8 (25.8%)	0.23
≥ 0.25	30 (58.8%)	23 (74.2%)	
Surgical procedure			
Wedge resection	32 (62.8%)	20 (64.5%)	1.00
Segmentectomy	19 (37.2%)	11 (35.5%)	
Pathological tumor stage			
1a/1b	49 (96.1%)	23 (74.2%)	<0.01
2a	2 (3.9%)	8 (25.8%)	
Histological differentiation			
Grade 1	42 (82.4%)	17 (54.8%)	0.01
≥ Grade 2	9 (17.6%)	14 (45.2%)	
pl			
Negative	50 (98.0%)	25 (80.7%)	0.01
Positive	1 (2.0%)	6 (19.3%)	
ly			
Negative	51 (100.0%)	29 (93.6%)	0.14
Positive	0 (0.0%)	2 (6.4%)	
v			
Negative	49 (96.1%)	26 (83.9%)	0.10
Positive	2 (3.9%)	5 (16.1%)	
Histological subtype			
Non-invasive	14 (27.5%)	4 (12.9%)	0.17
Invasive	37 (72.5%)	27 (87.1%)	
EGFR†			
Wild type	17 (53.1%)	13 (59.1%)	0.78
Mutant	15 (46.9%)	9 (40.9%)	

†Cases in which data were available. CEA, carcinoembryonic antigen; ly, lymphatic invasion; pl, pleural invasion; STAS, spread through air spaces; v, vascular invasion.

positive for STAS. Although the rate of STAS differs among studies, the frequency of STAS in resected early-stage lung adenocarcinoma patients in this study was consistent with previous reports (range: 14.8–52.4%).<sup>6,11,12,21</sup> Furthermore, STAS was significantly associated with malignant pathological characteristics, such as advanced tumor stage, lower histological differentiation, and the presence of pleural invasion. This result is also consistent with previous reports of STAS,<sup>6,10–12</sup> and collectively, this evidence

suggests that lung adenocarcinomas with STAS might be potentially malignant.

With regard to postoperative survival, our analyses showed that patients with STAS exhibited significantly poorer RFS and OS than those without. Furthermore, STAS was an independent prognostic parameter for RFS (hazard ratio 9.74;  $P < 0.01$ ), but not for OS. Previous reports regarding the prognostic role of STAS have shown that it negatively impacts postoperative survival in patients with resected lung



Number at risk					Number at risk							
STAS- (n=51)	51	50	40	18	6	STAS- (n=51)	51	50	40	19	8	2
STAS+ (n=31)	31	24	17	6	3	STAS+ (n=31)	31	29	20	6	3	

**Figure 1** Kaplan–Meier curves according to spread through air spaces (STAS). (a) Recurrence-free survival (RFS) and (b) overall survival (OS) rates were significantly poorer in patients with STAS than without ( $P < 0.01$  and  $P = 0.02$ , respectively). — STAS- ( $n = 51$ ), — STAS+ ( $n = 31$ ).

**Table 3** Univariate and multivariate analyses of the relationship between recurrence-free survival and clinicopathological factors

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (years)						
< 70	1.00					
≥ 70	1.18	0.34–4.61	0.80			
Gender						
Female	1.00					
Male	1.22	0.34–4.38	0.76			
Smoking status						
Never-smoker	1.00					
Smoker	1.53	0.44–5.99	0.51			
CEA (ng/mL)†						
≤ 3.2	1.00			1.00		
> 3.2	4.51	1.28–17.68	0.02	6.78	1.63–35.95	< 0.01
Surgical procedure						
Wedge resection	1.00					
Segmentectomy	0.56	0.12–2.06	0.40			
Pathological tumor stage						
1a/1b	1.00					
2a	3.09	0.66–11.15	0.14			
Histological differentiation						
Grade 1	1.00			1.00		
≥ Grade 2	16.00	3.92–107.53	< 0.01	15.43	3.14–126.73	< 0.01
pl						
Negative	1.00					
Positive	2.59	0.39–10.40	0.28			
ly						
Negative	1.00					
Positive	4.24	0.23–22.68	0.25			
v						
Negative	1.00					
Positive	3.65	0.55–14.77	0.16			
STAS						
Negative	1.00			1.00		
Positive	18.02	3.38–332.25	< 0.01	9.74	1.78–181.19	< 0.01

†Cases in which data were available. CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; ly, lymphatic invasion; pl, pleural invasion; STAS, spread through air spaces; v, vascular invasion.

**Table 4** Recurrence type according to STAS

Type of recurrence	N = 82	STAS (n = 82)		P
		Negative (n = 51)	Positive (n = 31)	
None	72 (87.8%)	50 (98.0%)	22 (71.0%)	< 0.01
Locoregional	9 (11.0%)	1 (2.0%)	†/8 (25.8%)‡	
Distant	1 (1.2%)	0 (0.0%)	§/1 (1.2%)§	

†Ipsilateral lymph node metastasis. ‡Surgical margin recurrence (3 cases); pulmonary metastasis (1 case); lymph node metastasis (3 cases); pleural dissemination (1 case). §Brain and bone metastasis. STAS, spread through air spaces.

adenocarcinoma and squamous cell carcinoma.<sup>6,11–15</sup> Kadota *et al.* reported that STAS is significantly associated with recurrence in early-stage adenocarcinoma after limited resection, but not lobectomy.<sup>6</sup> In addition, Shiono *et al.* reported that STAS is a prognostic factor in lung cancer patients undergoing sublobar resection, although this study included non-adenocarcinoma and pathological stages I–III.<sup>17</sup> In contrast, two further reports showed that STAS is a significant prognostic factor for postoperative survival in patients with pulmonary adenocarcinomas treated with lobectomy, but not wedge resection.<sup>12,20</sup> The prognostic impact of STAS in lung adenocarcinoma differs between published reports, thus future studies, specifically prospective studies, are warranted to elucidate the exact significance of STAS in lung adenocarcinoma patients treated with limited resection.

Furthermore, we demonstrated that STAS is significantly associated with recurrence, particularly locoregional recurrence, which was observed in nine (11.0%) patients and all but one were positive for STAS. Importantly, surgical margin recurrence was identified in three patients (3.7%) who were all positive for STAS. This result is consistent with the findings of previous studies, and a surgical margin distance < 1 cm is reported to be a risk factor for local recurrence.<sup>6,17,22</sup> In addition, Morimoto *et al.* demonstrated that the distance between the furthest edge of free-tumor cells and main tumors did not exceed the diameter of the main tumor in each case, with the average distance being 7.3 mm.<sup>15</sup> This evidence suggests that an insufficient margin with STAS may lead to local recurrence after limited resection and to achieve curative resection in STAS-positive lung cancer, the resection margin should be wider. Furthermore, if STAS could be predicted preoperatively, the optimum surgical procedure could be applied. Future studies should focus on this critical point.

There are several limitations and concerns associated with the present study. First, this is a single-institutional retrospective study and the patient sample analyzed was small (n = 82). Second, this study did not analyze the surgical margin distance, which might affect local recurrence, as mentioned above. Therefore, future studies should be conducted to clarify this issue. Finally, the surgical procedure and

pathological preparation method applied might affect the frequency of STAS, thus future studies should adopt precise pathological slide preparation protocol and surgical handling methods that minimize artifacts as much as possible.

In conclusion, STAS was predictive of poor postoperative survival in early-stage adenocarcinoma patients treated via limited resection and was associated with surgical margin recurrence.

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## Disclosure

No authors report any conflict of interest.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1** Univariate and multivariate analyses of the relationship between overall survival and clinicopathological factors.