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Clinical implication of tumour spread through air spaces in pathological stage I lung adenocarcinoma treated with lobectomy

Eunjue Yi[a,†], Jeong Hyeon Lee [b,†], Younggi Jung [a], Jae Ho Chung[a], Youngseok Lee[b] and Sungho Lee[a,*]

[a] Department of Thoracic and Cardiovascular Surgery, Korea University Anam Hospital, Seoul, Korea
[b] Department of Pathology, Korea University Anam Hospital, Seoul, Korea

* Corresponding author. Department of Thoracic and Cardiovascular Surgery, Korea University Anam Hospital, 73, Koryeodae-ro, Seongbuk-gu, Seoul 02841, Korea. Tel: +82-2-9205436; fax: +82-2-9205369; e-mail; sholeemd@korea.ac.kr (S. Lee).

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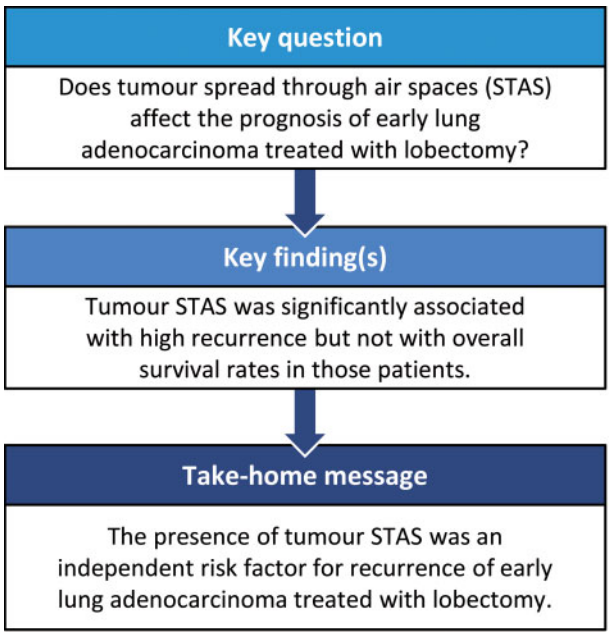

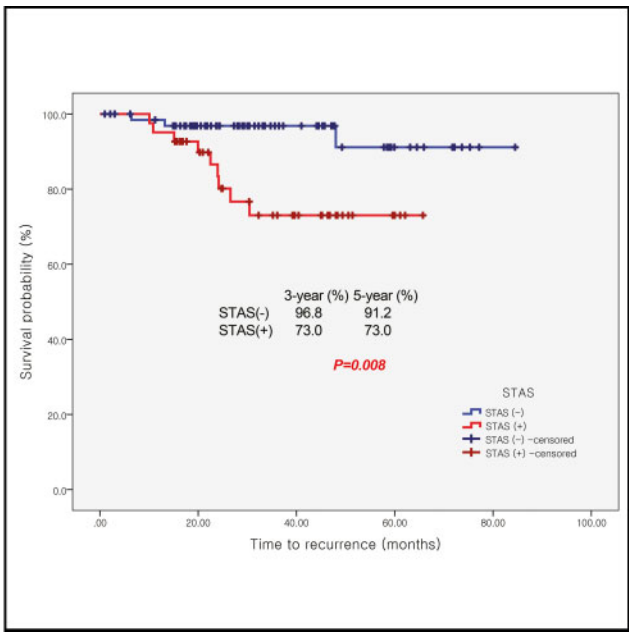

Abstract

OBJECTIVES: The aim of this study was to evaluate the clinical implication of tumour spread through air spaces (STAS) as a prognostic factor in pathological stage I lung adenocarcinoma treated with lobectomy and to identify related parameters.

METHODS: Medical records of patients who underwent pulmonary lobectomy for stage I (American Joint Committee on Cancers eighth edition) lung adenocarcinomas between 2012 and February 2018 at our institutions were reviewed retrospectively. Patients with minimally invasive adenocarcinomas and tumours ≥3 cm in size were excluded. Included patients were classified into STAS (+) and STAS (-) groups. Clinical implications of STAS and recurrence in patients were investigated.

RESULTS: A total of 109 patients was analysed: 41 (37.6%) in the STAS (+) and 68 (62.4%) in the STAS (-) group. STAS was associated with larger consolidation diameter on chest tomography (≥1.5 cm; $P = 0.006$) or a higher invasive ratio (≥85%; $P = 0.012$) and presence of a micropapillary pattern in multivariable analysis ($P = 0.003$) The recurrence-free survival curve showed statistical difference ($P = 0.008$) with

[†]The first two authors contributed equally to this work.

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3-year survival rates of 73.0% (9 patients) and 96.8% (2 patients) in the STAS (+) and STAS (-) group, respectively. However, no statistical significance was observed in the lung cancer-related survival curve ($P = 0.648$). The presence of STAS was an independent risk factor for recurrence in multivariable analysis (hazard ratio = 5.9, $P = 0.031$).

CONCLUSIONS: The presence of STAS could be an important risk factor for recurrence in patients with early-stage invasive lung adenocarcinoma treated with pulmonary lobectomy.

Keywords: Invasive adenocarcinoma • Lobectomy • Prognosis

ABBREVIATIONS

AIS	Adenocarcinoma *in situ*
Chest CT	Chest computed tomography
MIA	Minimally invasive adenocarcinoma
STAS	Spread through air spaces

INTRODUCTION

Tumour spread through air spaces (STAS) is a newly adopted pathological pattern of invasion of cancer cell nests spreading into air spaces in the lung parenchyma adjacent to the border of the main tumour [1–3]. Studies have reported that STAS is an independent risk factor for loco-regional recurrence in small early-stage lung adenocarcinoma treated with limited resection [4–6] and a negative survival risk factor for surgically resected stage I squamous cell lung cancers [7]. However, STAS has not been proved to be a risk factor for recurrence in early-stage lung cancer treated with lobectomy.

As imaging technology advances and adoption of screening tests for lung cancer expands, detection of small, peripheral early-stage lung cancers that could be candidates for limited resection is increasing [8]. The negative correlation between STAS and recurrence rate suggests an important indicator for treatment strategies.

The presence of STAS has been reported to be related to invasive pathological characteristics such as larger tumour size, visceral pleural invasion micropapillary and solid predominant subtypes [4, 5]. We found that some patterns of early-stage lung adenocarcinoma such as adenocarcinoma *in situ* (AIS) or minimally invasive adenocarcinoma (MIA) are weakly related to the presence of STAS, and most advanced adenocarcinomas are strongly associated with STAS. We were interested in the clinical manifestation of early-stage invasive lung cancers presenting STAS, <3 cm in total size (including lepidic portion) with contained invasive portions larger than 5 mm.

In this study, we investigated the prognostic influence of STAS in early-stage invasive lung adenocarcinoma in patients treated with lobectomy. We investigated the precise clinical implications of STAS in early-stage patients who underwent standard surgical treatments.

MATERIALS AND METHODS

Patient characteristics

A retrospective medical review of 230 patients who underwent surgical treatment for lung adenocarcinoma between January 2012 and February 2018 at Korea University Anam Hospital was performed. Clinical and pathological stages were revised according to the eighth edition of the American Joint Committee on Cancers (AJCC)/Union for International Cancer Control (UICC) lung cancer staging system with 183 patients included in stage I [9, 10]. We excluded patients who (i) had a tumour larger than 3 cm in total tumour size including lepidic portion (33 patients); (ii) were diagnosed as having AIS (10 patients) or MIA (14 patients); or (iii) underwent sublobar resection (15 with wedge resection and 1 with segmentectomy).

Analysed patients were classified into 2 groups by the presence of STAS. Demographic information, preoperative findings, pathological results and follow-up clinical manifestations were reviewed and compared.

Pathology review

All archival slides and pathology reports of patients were reviewed by 2 specialized pulmonary pathologists (J.H.L. and Y.L.). The presence of STAS and relevant pathological features including micropapillary pattern, lymphovascular invasion or inflammatory reactions and invasion of visceral pleura were investigated.

The definition of STAS was based on research from Kadota *et al.* [4] (i.e. tumour cells within air spaces; Fig. 1), with (i) micropapillary structures of papillary structures without central fibrovascular cores, (ii) solid nests or tumour islands of solid collections of tumour cells filling air spaces and (iii) scattered discohesive single cells. The distance from the edge of a tumour to the farthest STAS was measured using a ruler as well as using numbers of in-between alveolar space.

Categorization of AIS, MIA, differentiation and predominant subtypes of adenocarcinoma followed the new adenocarcinoma classification system of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society [11].

Tumour sizes were measured in 2 ways. Before surgery, the largest diameter of total tumour size and the consolidative part were measured using chest computed tomographic imaging (chest CT). After surgery, total tumour size and invasive tumour size (excluding lepidic portion and invasive component only) were measured from pathological specimens. The total tumour size from the imaging study was defined as the largest diameter of the tumour including ground-glass opacity, and that from the pathological specimen, including the lepidic portion.

The consolidative tumour (CT) ratio was the proportion of consolidative size divided by total size measured on chest CT. The invasive ratio was invasive size divided by total size.

Clinical prognosis

All patients who underwent surgical resection for lung cancer were followed up regularly by the outpatient department.

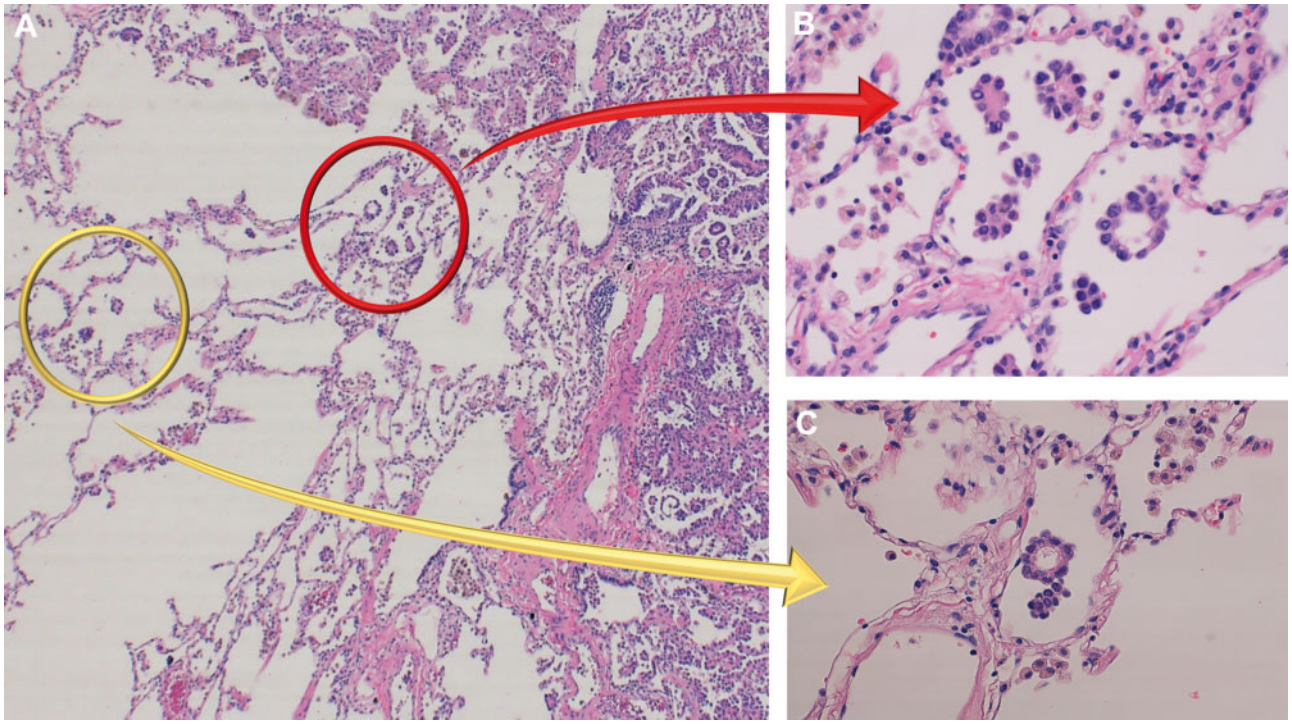

Figure 1: Pathological findings of spread through air spaces (STAS). (**A**) High-power field image (×100) of lung adenocarcinoma. Tumour margin and normal alveolar spaces are observed. (**B**) STAS adjacent to the edge of tumours (red arrow). STAS are defined as (i) micropapillary structures consisting without central fibrovascular cores, (ii) solid nests or tumour island filing air spaces, and (iii) single cells consisting of scattered discohesive single cells. (**C**) STAS found within air spaces in the lung parenchyma beyond the edge of the main tumour (yellow arrow).

Medical examination including chest CT was scheduled every 4 months after surgery during the first 2 years and then every 6 months for the next 3 years.

Recurrence was confirmed when radiological or pathological evidence was reported. Loco-regional recurrence was defined as evidence of a tumour identified within the diseased hemithorax, ipsilateral lung, ipsilateral mediastinal or hilar lymph nodes. Distant metastasis was any recurrence site outside the ipsilateral haemothorax including contralateral lung and hilum [12, 13]. Simultaneous loco-regional and distant metastases were categorized as loco-regional.

Statistical analysis

χ^2 and Fisher's exact tests (when the expected value of data was lower than 5) were used for statistical comparison for categorical variables. Student's *t*-test for parametric and Mann–Whitney *U*-test for non-parametric variables were applied to compare continuous variables. Univariable analysis was performed to identify statistically significant variables for recurrence using Cox's proportional hazard model and STAS presentation using a logistic regression method. Multivariable analysis was performed with variables found to be significantly related to recurrence using Cox's proportional hazard model and STAS presentation, a logistic regression method.

Cumulative recurrence-free, cancer-related and overall survival rates were calculated using the Kaplan–Meier method, and statistical differences were determined using log-rank tests. All survivals were calculated assuming patients were alive with or without recurrence from the date of surgery. Significant differences were defined when the *P*-value was <0.05 with 5% significance level. Statistical analyses were performed using SPSS 20.0 (SPSS Inc., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 109 patients with pathological stage I lung adenocarcinoma with total tumour sizes (including lepidic portion) <3 cm was analysed in this study. The STAS (+) group had 41 patients and the STAS (-) group had 68 patients. All enrolled patients underwent lobectomy with mediastinal node dissection (including at least 3 mediastinal and 2 hilar lymph node stations). The mean follow-up was 37.5 ± 19.68 months. Demographic and preoperative characteristics are in Table 1.

Relating factors with spread through air spaces

Pathological characteristics and perioperative data of the STAS (+) and STAS (-) groups are shown in Table 2 (and Supplementary Material, D1). Univariable and multivariable analysis searching for factors related to STAS are shown in Table 3. Larger consolidative size on chest CT or higher invasive ratio was significantly related to the presence of STAS, as was the presence of a micropapillary pattern. Pathological stages showed no prognostic power for STAS nor recurrence in multivariable analysis (Tables 3 and 4). The full data of univariable analysis for risk factors of STAS are given in the Supplementary Material, D2.

Table 1: Patient characteristics and preoperative findings

Variables	STAS (+) (*N* = 41) *N* (%)		STAS (-) (*N* = 68) *N* (%)		Total (*N* = 109) *N* (%)		*P*-value
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Age (years)	66.1 ± 7.92	63.6–68.6	63.3 ± 9.88	70.1–65.7	64.4 ± 9.12	62.6–66.1	0.147
Gender							0.541
Men	28 (68.3)		26 (38.2)		39 (35.8)		
Women	13 (31.7)		42 (61.8)		70 (64.2)		
Smoking							0.919
Never	31 (73.4)		49 (72.1)		80 (73.4)		
Ex	8 (19.5)		15 (22.1)		23 (21.1)		
Current	2 (4.9)		4 (5.9)		6 (5.5)		
PPY	32.4 ± 19.14	19.5–45.3	28.9 ± 19.14	19.7–38.2	30.2 ± 18.53	23.1–37.2	0.645
Comorbidities							
Hypertension	22 (37.6)		26 (54.2)		48 (44.0)		0.116
Diabetes mellitus	7 (17.1)		11 (16.2)		18 (16.5)		1.000
Atrial fibrillation	2 (4.9)		3 (4.4)		5 (4.6)		1.000
Angina	7 (17.1)		2 (2.9)		9 (8.3)		0.025
Heart failure	3 (7.3)		2 (2.9)		5 (4.6)		0.362
Liver cirrhosis	0 (0.0)		2 (2.9)		2 (1.8)		0.526
Renal insufficiency	2 (4.9)		4 (5.9)		6 (5.5)		1.000
Stroke	0 (0.0)		3 (4.4)		3 (2.8)		0.290
COPD	1 (2.4)		3 (4.4)		4 (3.7)		1.000
Interstitial pneumonitis	5 (12.2)		0 (0.0)		5 (4.6)		0.013
Double primary cancer							0.574
Lung	2 (4.9)		1 (1.5)		3 (2.8)		
Other organs	11 (26.8)		19 (27.9)		30 (27.5)		
CCI	3.2 ± 1.49	2.8–3.7	2.9 ± 1.99	2.4–3.3	3.0 ± 1.82	2.7–3.3	0.107
Preoperative PFT							
FEV1	2.3 ± 0.55	2.1–2.5	2.5 ± 0.51	2.3–2.6	2.4 ± 0.54	2.3–2.5	0.113
FEV1 (%)	90.0 ± 16.49	84.8–95.2	93.6 ± 14.65	90.0–97.1	92.2 ± 15.39	89.3–95.2	0.237
DLCO	15.4 ± 3.18	14.4–16.5	16.8 ± 4.02	15.8–17.9	16.3 ± 3.76	15.5–17.1	0.109
DLCO (%)	67.8 ± 30.05	57.9–77.7	63.5 ± 32.18	55.2–71.8	65.2 ± 31.09	58.9–71.4	0.511
CT diameter							
Total diameter	21.0 ± 4.94	19.5–22.6	19.0 ± 4.90	17.8–20.2	19.8 ± 4.99	18.8–20.7	0.051
<2.0 cm	16 (39.0)		33 (48.5)		49 (45.0)		0.427
≥2.0 cm	25 (61.0)		35 (51.5)		60 (55.0)		
Solid	19.5 ± 5.04	17.9–21.1	14.7 ± 6.27	13.1–16.2	16.5 ± 6.27	15.3–17.7	<0.001
1.5 cm	10 (48.6)		43 (63.2)		53 (48.6)		<0.001
≥1.5 cm	31 (75.6)		25 (36.8)		56 (51.4)		
CT ratio	0.9 ± 0.12	0.89–0.97	0.76 ± 0.23	0.70–0.81	0.82 ± 0.21	0.78–0.86	<0.001
<85%	8 (19.5)		40 (58.8)		48 (44.0)		<0.001
≥85%	33 (80.5)		28 (41.2)		61 (56.0)		
CT location							1.000
Parenchymal	16 (39.0)		26 (38.2)		42 (38.5)		
Peripheral	25 (61.0)		42 (61.8)		67 (61.5)		
Clinical stage							
T stages							0.277
1a	2 (4.9)		4 (5.9)		6 (5.5)		
1b	9 (22.0)		23 (33.8)		32 (29.4)		
1c	3 (7.9)		3 (4.4)		6 (5.5)		
2a	25 (61.0)		38 (55.9)		63 (57.8)		
3	2 (4.9)		0 (0.0)		2 (1.8)		
N stages							
N0	39 (95.1)		67 (98.5)		106 (97.2)		
N1	2 (4.9)		1 (1.5)		3 (2.8)		
IA1	0 (0.0)		1 (1.5)		1 (0.9)		0.195
IA2	11 (26.8)		26 (38.2)		37 (33.9)		
IA3	2 (4.9)		3 (4.4)		5 (4.6)		
IB	25 (61.0)		37 (54.4)		62 (56.9)		
IIA	0 (0.0)		1 (1.5)		1 (0.9)		
IIB	3 (2.8)		0 (0.0)		3 (2.8)		

CCI: Charlson comorbidity index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CT: consolidative tumour; DLCO: diffuse capacity of lung for carbon monoxide; FEV1: forced expiratory volume in 1 s; PFT: pulmonary function test; PPY: pack per year; SD: standard deviation; STAS: spread through air spaces.

Table 2: Major perioperative findings

Variables	STAS (+) (*N* = 41) *N* (%)		STAS (-) (*N* = 68) *N* (%)		Total (*N* = 109) *N* (%)		*P*-value
	Mean ± SD	95% CI	Mean ± SD	95% CI	Mean ± SD	95% CI	
Predominant							0.005
Lepidic	0 (0.0)		19 (27.9)		19 (17.4)		
Acinar	30 (73.2)		36 (52.9)		66 (60.6)		
Papillary	5 (12.2)		3 (4.4)		8 (7.3)		
Micropapillary	2 (4.9)		1 (1.5)		3 (2.8)		
Solid	1 (2.4)		3 (4.4)		4 (3.7)		
Mucinous adenocarcinoma	3 (7.3)		3 (8.8)		9 (8.3)		
Diameter							
Total	21.0 ± 4.94	19.5–22.6	19.0 ± 4.90	17.8–20.2	19.8 ± 4.99	18.8–20.7	0.098
<2.0 cm	18 (43.9)		36 (52.9)		54 (49.5)		0.430
≥2.0 cm	23 (56.1)		32 (47.1)		55 (50.5)		
Invasive	19.5 ± 5.04	17.9–21.1	14.7 ± 6.30	13.1–16.2	16.5 ± 6.27	15.3–17.7	0.003
<1.5 cm	10 (24.4)		33 (48.5)		43 (39.4)		0.015
≥1.5 cm	31 (75.6)		35 (51.5)		66 (60.6)		
Invasive ratio	0.9 ± 0.12	0.89–0.97	0.8 ± 0.23	0.70–0.81	0.8 ± 0.21	0.78–0.86	0.003
<85%	3 (7.3)		29 (42.6)		32 (29.4)		<0.001
≥85%	38 (92.7)		39 (57.4)		77 (70.6)		
Pathological features							
Visceral pleural invasion							0.058
P0	15 (36.6)		29 (42.6)		44 (40.4)		
P1	21 (51.2)		38 (55.9)		59 (54.1)		
P2	5 (12.2)		1 (1.5)		6 (5.5)		
Vascular invasion	3 (7.3)		2 (2.9)		5 (4.6)		0.362
Lymphatic invasion	3 (7.3)		3 (4.4)		6 (5.5)		0.670
Necrosis	6 (14.6)		7 (10.3)		13 (11.9)		0.550
Micropapillary pattern							
Positive	29 (70.7)		12 (17.6)		41 (37.6)		<0.001
STAS							
Distance (mm)	0.6 ± 1.02	0.4–0.8					
Alveolar space	2.4 ± 3.82	1.69–3.14					
Pathological stage							0.109
IA2 (T1bN0)	7 (17.1)		23 (33.8)		30 (27.5)		
IA3 (T1cN0)	8 (19.5)		7 (10.3)		15 (13.8)		
IB (T2aN0)	26 (63.4)		38 (55.9)		64 (58.7)		
EGFR							1.000
Positive	17.0		35.0		52.0		
Exon18	0.0		1.0		1.0		0.907
Exon19	7.0		17.0		24.0		
Exon21	9.0		16.0		25.0		
Multiple variant	1.0		1.0		2.0		
ALK							0.801
Positive	5.0		6.0		11.0		
Negative	19.0		35.0		54.0		
ALK (%)	8.5 ± 11.24	4.9–12.0	9.2 ± 13.83	3.4–15.1	8.7 ± 12.16	5.7–11.8	0.823

ALK: anaplastic lymphoma receptor tyrosine kinase; CI: confidence interval; EGFR: epidermal growth factor receptor; SD: standard deviation; STAS: spread through air spaces.

Survival analysis

Total recurrence rates were 11.0% (12 patients, Supplementary Material, D3). Univariable and multivariable analyses of recurrence-free survival were performed (Supplementary Material, D4 and Table 4). The presence of STAS and more than 10% micropapillary pattern were significant risk factors for recurrence. The recurrence-free survival curve showed statistical difference with a *P*-value of 0.008 (log-rank test), 3-year survival rates of 73.0% (9 patients) in STAS (+) and 96.8% (2 patients) in STAS (-) group. However, no statistical significance was observed in the lung cancer-related survival curve ($P = 0.648$ in log-rank test) with 97.6% (1 patient) in the STAS (+), and 97.0% (2 patients) in the STAS (-) group. The results recurrence-free and overall survival analyses are in shown in the Supplementary Material, D5 and Fig. 2. From the logistic regression test, the recurrence rate at any site in the STAS (+) group was significantly higher than in the STAS (-) group (9% and 22% vs 3% and 4.4%, $P = 0.009$) but only for loco-regional recurrence (8% and 19.5% vs 1% and 1.5%, $P = 0.002$) and not for distant metastasis ($P = 1.000$, Supplementary Material, D3).

DISCUSSION

We investigated the prognostic ability of STAS in early-stage lung adenocarcinoma for invasive tumours larger than 5 mm but not exceeding 3 cm in total tumour size for patients treated with standard major pulmonary resection. Our study showed a correlation between higher recurrence rates and the presence of STAS in those patients. The 5-year recurrence-free survival values for any

Table 3: Univariable and multivariable analysis for identifying independent risk factors for the presence of STAS

Variables		Univariable analysis			Multivariable analysis		
		Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
CT diameter							
Total diameter		1.1	1.00–1.18	0.044			
Consolidation	≥1.5 cm	6.8	2.38–19.39	<0.001	1.44	1.108–1.862	0.006
CT ratio (%)	≥85%	5.9	2.37–14.65	<0.001			
Diameter							
Invasive	≥1.5 cm	3.2	1.31–7.62	0.010			
Invasive ratio	≥85%	6.9	2.20–21.47	0.001	1.11	1.024–1.212	0.012
Pathological features							
Visceral pleural invasion	P2	9.7	1.03–90.41	0.047			
Micropapillary pattern	Positive	11.3	4.51–28.22	0.000	6.09	1.826–20.284	0.003
Pathological stage	IA3	3.8	1.00–14.07	0.050			

CI: confidence interval; CT: consolidative tumour; STAS: spread through air spaces.

Table 4: Univariable and multivariable analysis for identifying independent risk factors for recurrence in any sites during follow-up periods

Variables	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age						
>65	5.0	1.11–23.16	0.036	5.4	0.87–33.35	0.070
Gender						
Men	5.8	1.63–20.49	0.007	3.9	0.86–17.24	0.078
Smoking						
Current/ex	3.6	1.12–11.4	0.032			
PPY	1.0	1.00–1.06	0.043			
CT diameter						
Total diameter	1.2	1.05–1.35	0.009			
≥2.0 cm	4.8	1.05–22.03	0.043			
Solid	1.2	1.09–1.41	0.001			
≥1.5 cm	2.0	0.57–7.23	0.269			
CT ratio (%)	1.1	1.00–1.13	0.045	6.9	0.72–65.63	0.095
≥85%	9.6	1.23–74.42	0.031			
Diameter						
Total	1.2	1.08–1.44	0.003			
≥2.0 cm	5.4	1.19–24.77	0.029			
Invasive	1.2	1.08–1.38	0.002			
≥1.5 cm	7.5	0.96–57.90	0.054			
Pathological features						
Lymphatic invasion	10.4	1.83–59.52	0.008			
Micropapillary pattern						
Positive	10.6	2.20–51.53	0.003			
STAS	4.9	1.33–18.18	0.017	5.9	1.18–30.09	0.031
Distance	1.6	1.02–2.63	0.040			
Changes in stages						
Up	4.7	1.25–17.54	0.022			

CI: confidence interval; CT: consolidative tumour; PPY: pack per year; STAS: spread through air spaces.

recurrences and loco-regional recurrence were significantly lower in the STAS (+) than the STAS (-) group (Fig. 2).

Results from our study seemed to be contrary to the conclusions of previous studies [4]. This difference could be due to the fact that we excluded AIS and MIA and instead included larger tumours (<3 cm). When we excluded larger tumours and included AIS or MIA, similar to other studies, we found no statistical differences in recurrence between the STAS (+) and (-) groups (STAS positive 18 and STAS negative 46, $P = 0.447$).

Therefore, a certain amount of invasive component (tumour with an invasive component larger than 5 mm) was thought to be related to the presence of STAS. Although the visual appearance of STAS was of 'tumour islands' floating in alveolar spaces, the islands were known to be interconnected to each other and attached to the main tumour [14, 15]. Therefore, early lung adenocarcinoma, which consists of mostly non-invasive components, was not expected to be related to STAS. We found neither STAS nor recurrence in any excluded cases of AIS or MIA in our study.

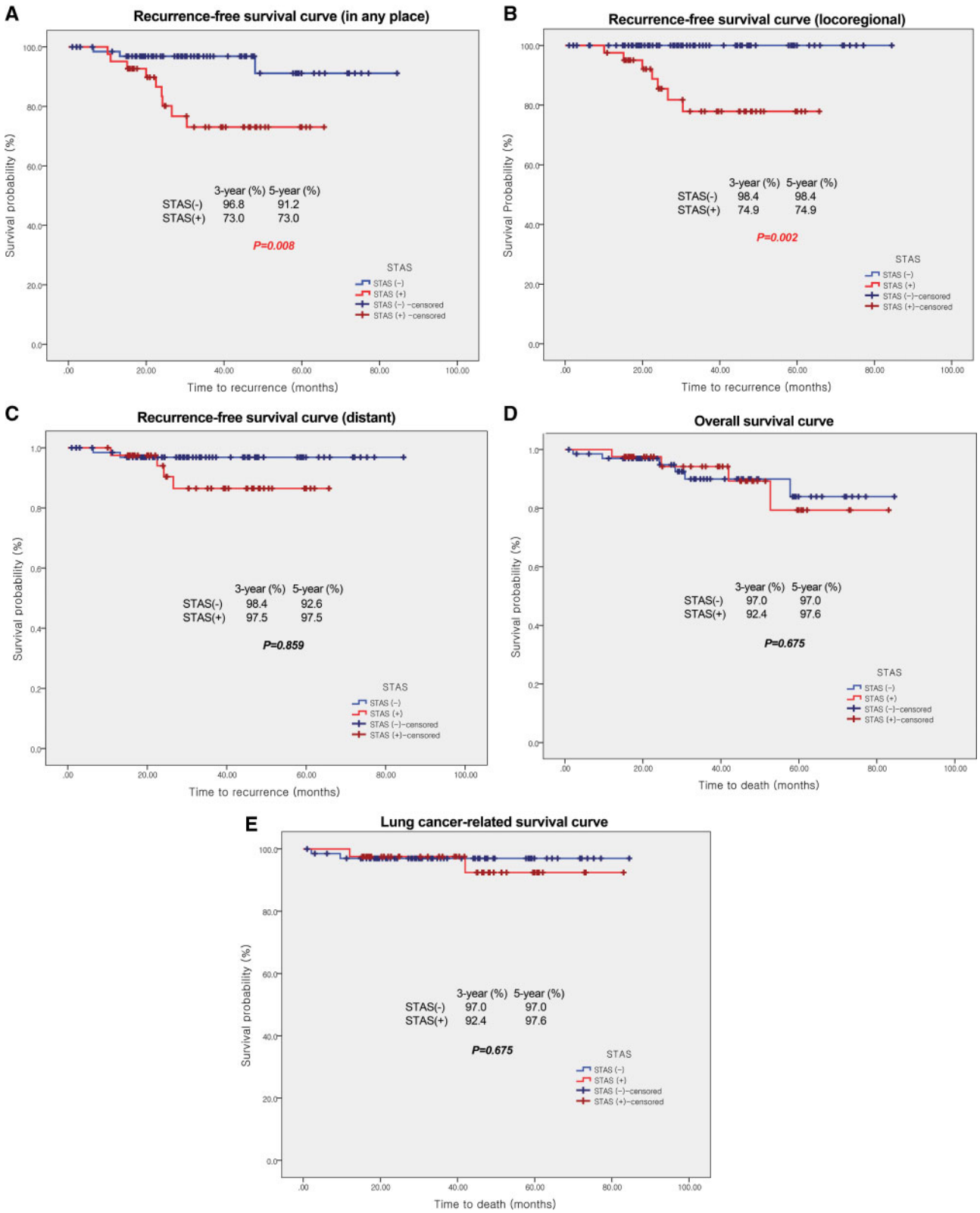

Figure 2: Recurrence-free and overall survival curves of STAS (+) and STAS (-) groups. (**A**) Recurrence-free survival curve in any place. (**B**) Recurrence-free survival curve related with loco-regional recurrence. (**C**) Recurrence-free survival curve related with distant metastasis. (**D**) Overall survival curve. (**E**) Lung cancer-related overall survival. Number of patients with recurrence and mortality was described in Supplementary Material, D3. Results of Kaplan–Meier survival analysis with log-rank tests were described in Supplementary Material, D5. STAS: spread through air spaces.

Our hypothesis was supported by the results of the multivariable analysis for risk factors of STAS. Two pathological components of invasive ratio, meaning the proportion of the invasive part of the total tumour size, and micropapillary pattern showed a correlation with STAS. A higher invasive ratio seemed to be correlated with a higher probability of STAS positivity. Only 4

patients (9.85%) in the STAS (+) group had an invasive ratio <0.85, while 29 in the STAS (-) group (42.9%) did. All STAS (+) patients showed a higher than 0.5 invasive ratio (mean ratio 0.96 ± 0.08, range 0.59–1.0), while negative patient ratios were from 0.18 to 1.0 (mean ratio 0.81 ± 0.23). This finding could imply that STAS was important in the early phase of the invasion.

The relevance of STAS and micropapillary patterns has been reported [4, 16]. Micropapillary patterns were referred to as independent risk factors of recurrence before STAS was identified [17–19]. STAS is occasionally suspected as an early form or misinterpretation of micropapillary patterns [4, 17]. The presence of STAS could precede an invasion mechanism, with other invasive features appearing subsequently [20]. Micropapillary patterns and invasive tumour size could be a feature of mature invasion in lung adenocarcinoma. Currently, few question the existence of STAS, and the micropapillary pattern is considered a pathological factor that is intimately related to STAS [21].

We expect certain genetic mutations will be related. Although we found no correlation with any epidermal growth factor receptor mutations in our study as the study of Toyokawa *et al.* [22], studies report lower rates of epidermal growth factor receptor mutations [23] and higher BRAF [21] and k-ras mutations [2, 23].

Limitations

Our research has several limitations. First, this was a retrospective study at a single institute with a small study population with its inherent selection bias. As a result, pathological stages (IA2, IA3 or IB) which were proved to be obvious prognostic factors showed no statistical significance in our study. Similarly, invasive tumour size showed no prognostic significance for recurrence in multivariable analysis. Also, only 109 patients were not sufficient to prove prognostic power [24] of other histological features including the influence of predominant subtype or differentiation. Moreover, quantitative analysis of STAS could not be performed as we had not measured the amount. The number of STAS sites spreading over the tumour edge has a leading function in recurrence [22], and measuring the quantitative effects of STAS is important.

Our study involved controversies related to *ex vivo* artefacts. The presence of free-floating tumour cell clusters was possibly due to surgical collapse, smooth muscle contraction of lung specimens or spread through knife surface [25, 26]. However, no definite differentiation standards with artefacts exist, and reporting of proven relationships between free-floating cells in alveolar space and negative long-term outcomes cannot be explained by artefacts alone [21].

Finally, our results were possibly due to inadequate regional lymph node dissection, since the prevalence of local recurrence was significantly associated with nodal status [13]. Although our data showed qualified lymph node dissection (average number of hilar and mediastinal stations was 5, the average number of dissected nodes was 15.4), and only 2 cases of regional lymph node recurrence were found (Supplementary Material, D6), the completeness based on its definition [27] was questionable.

Several issues related to STAS need to be addressed. Factors that contribute to the genesis of STAS from the invasive component of adenocarcinoma need to be identified. Several lung cancer-related molecules and biomarkers including anaplastic lymphoma kinase and ROS1 rearrangement were associated with STAS [3]. The lead-lag relationship between STAS and micropapillary patterns should be examined more precisely. Preoperative or intraoperative identification of STAS will suggest an important clinical turning point.

The presence of STAS was not reported during frozen section analysis at our institute. The reason is largely because our pathologists worried about the presence of spread through the knife surface instead of STAS in frozen procedures; however, this limitation could restrict clinical importance. The identification of STAS during frozen procedures could change surgical methods intraoperatively.

Preoperative identification of STAS might shorten the clinical decision-making process. Preoperative identification would be helpful for determining the extent of surgical resection or a follow-up strategy. Our study found that a consolidative size larger than 1.5 cm on chest CT was highly related to the presence of STAS, which as correlated with the study of Toyokawa *et al.* [28]. An imaging study using multiplex immunofluorescence reconstructed 3-dimensional images of STAS attached to the alveolar wall adjacent to the main tumour [12]. Rapid advances in microscopic imaging techniques will contribute to preoperative or intraoperative detection of STAS.

CONCLUSION

The presence of STAS was an independent risk factor for recurrence in patients with pathological stage I lung adenocarcinoma (3 cm≤ total size, excluding MIA). Patients with STAS tended to have higher rates of loco-regional recurrence ($P = 0.001$). Relevant factors for STAS were larger consolidation on chest CT, larger invasive tumour size, higher invasive ratio and the presence of micropapillary patterns.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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Author contributions

Eunjue Yi: Conceptualization; Funding acquisition; Writing—original draft; Writing—review & editing. **Jeong Hyeon Lee:** Conceptualization; Formal

analysis; Resources; Writing—original draft. **Younggi Jung:** Data curation; Investigation. **Jae Ho Chung:** Investigation; Supervision. **Youngseok Lee:** Data curation; Investigation; Supervision. **Sungho Lee:** Conceptualization; Formal analysis; Supervision; Writing—review & editing.

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