Purpose

- Spread through air spaces (STAS) has been defined as spreading tumor cells through air spaces in the lung parenchyma beyond the edge of the tumor and recently been recognized as pathologic invasive pattern in the 2015 World Health Organization (WHO) Classification of Lung Tumors.

- Invasive mucinous adenocarcinoma (IMA) is a unique histological subtype of lung adenocarcinoma. Due to its low incidence rates, clinicopathologic and survival data for IMA is inadequate and often contradictory. Besides, there has been limited research regarding the prognostic relationship between STAS and IMA

- The purpose of this study is to investigate the clinicopathologic characteristics of IMA and evaluate whether STAS has an independent prognostic significance of disease recurrence in IMA.

- From January 2015 and December 2019, medical records of 133 patients retrospectively reviewed and categorized into STAS (-) group (n = 80) and STAS (+) group (n = 53).

- Primary outcome: Recurrence-free Survival (RFS)

- Secondary outcome: Recurrence pattern (Loco-regional recurrence and distant metastasis)

- Statistical analysis

  - Survival curves were plotted using the Kaplan–Meier method and compared with the log-rank test.

  - Stepwise multivariable Cox-regression analysis to assess the prognostic value of STAS

  - Inverse probability of treatment weight (IPTW) - adjusted log-rank test

❖ The 5-year RFS was 66.1% in the STAS (+) group and 91.8% in the STAS (-) group (P < .001), and the incidence of locoregional recurrence was significantly higher in the STAS (+) group than the STAS (-) group (1 [1.2%] vs 12 [22.6%], P < 0.001).
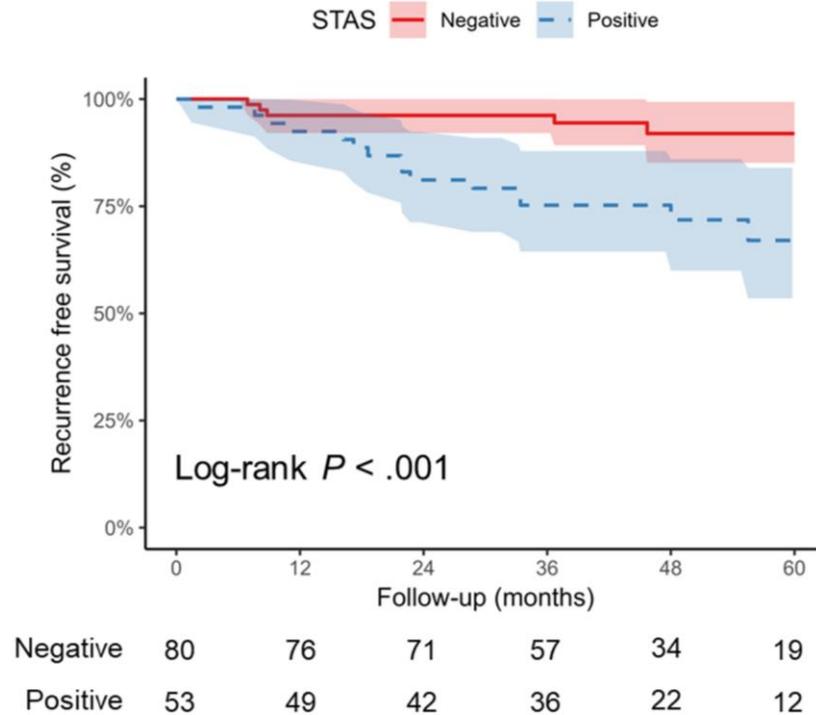
❖ Multivariable analysis revealed that STAS was associated with poor prognosis for all-recurrence (hazard ratio 2.81, 95% confidence interval 1.01 – 7.81, P = 0.048).

	Univariable	Multivariable	
	P value	HR (95% CI)	P
Age, years	0.026	1.08 (1.01 – 1.14)	0.015
Pathologic T stage	<.001		
T1		1 (reference)	
T2		3.86 (0.99 – 15.06)	0.051
T3, T4		12.98 (3.46 – 48.76)	<.001
Pathologic N stage	0.020		
N0		1(reference)	
N1, N2		6.91 (1.70 – 28.11)	0.007
STAS	0.002	2.81 (1.01 – 7.81)	0.048

❖ After IPTW adjustment, 5-year RFS was 66.3% in the STAS (+) group and 92.9% in the STAS (-) group (*P* = .010), and risk for locoregional recurrence was greater in the STAS (+) group than the STAS (-) group (1.1 [0.9%] vs 20.8 [16.6%], *P* < .001).

	STAS (-) [a]	STAS (+) [a]	SMD
	n = 127.9	n = 125.0	
Age, years	67.6 ± 9.4	68.0 ± 9.2	0.052
Sex,	56.4 (44.1)	60.0 (48.0)	0.078
Smokers	59.4 (46.5)	60.5 (48.4)	0.039
Diabetes mellitus, yes	26.8 (21.0)	31.2 (25.0)	0.095
Hypertension, yes	69.7 (54.5)	71.3 (57.1)	0.053
Malignancy other than	23.1 (18.1)	26.8 (21.4)	0.084
lung cancer			
FEV1, predicted %	106.0 ± 19.7	106.2 ± 18.4	0.009
Pathologic Tumor size	3.2 ± 2.4	3.40 ± 2.4	0.081
pT stage			0.036
pT1	71.5 (55.9)	68.9 (55.1)	
pT2	38.7 (30.3)	37.3 (29.8)	
pT3, T4	7.8 (6.1), 9.8 (7.6)	12.0 (9.6), 6.8 (5.4)	
pN stage			0.025
N0	119.9 (93.7)	117.9 (94.3)	
N1, N2	8.0 (6.3)	7.1 (5.7)	
Lympho-vascular invasion	22.7 (17.8)	24.8 (19.9)	0.053
Adjuvant Chemotherapy	17.4 (13.6)	14.5 (11.6)	0.061

	STAS (-) [a]	STAS (+) [a]	P-value [b]
	n = 127.9	n = 125.0	
Outcomes			
5-year RFS, %	92.9 ± 4.3	66.3 ±10.6	0.010
All-Recurrence	6.7 (5.2)	30.9 (24.7)	0.001
Locoregional	1.1 (0.9)	20.8 (16.6)	<.001
Distant	2.9 (2.3)	1.2 (0.9)	0.455
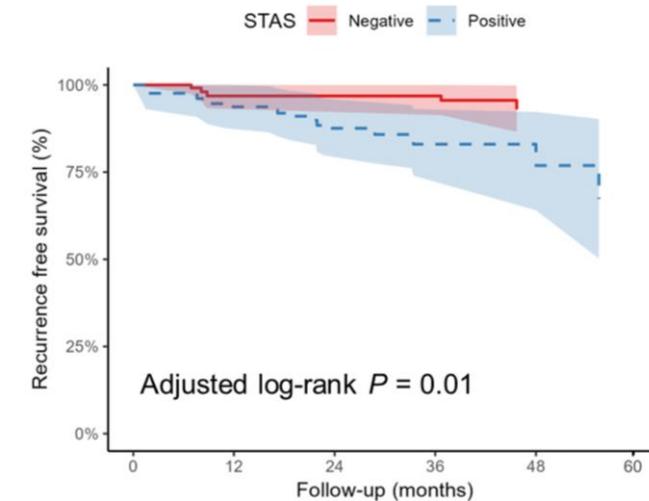
Negative	127.9	122.9	122.9	122.9	57.4	57.4
Positive	125.0	118.2	110.4	103.4	59.8	37.9

Conclusion

- STAS was observed in 39.1% (53 out of 133).

- The STAS (+) group shows larger tumor size (2.9 ± 2.4cm vs 3.8 ± 2.4cm, P = 0.031) and higher incidence of lympho-vascular invasion (6 [7.5%] vs 18 [34.0%], P < .001) compared to the STAS (-) group.

- The presence of STAS showed negative prognostic impact on disease recurrence after curative resection of IMA in univariate, multivariable and IPTW analysis. These results might be attributed to the higher locoregional recurrence rate in IMA with STAS compared to IMA without STAS.