



Clinical significance of spread through air spaces according to *EGFR* mutation status in lung adenocarcinoma

Asato Hashinokuchi¹, Naoki Haratake¹, Shinichiro Shimamatsu¹, Takuro Kometani¹, Toshiaki Kawabata¹, Ryo Toyozawa¹, Kenichi Taguchi², Masafumi Yamaguchi

¹ Department of Thoracic Oncology, NHO Kyushu Cancer Center, Fukuoka, Japan, ² Department of Pathology, NHO Kyushu Cancer Center, Fukuoka, Japan

Correspondence: asato.hashinokuchi.surg@gmail.com

INTRODUCTION

- **Spread through air spaces (STAS)** is a poor prognostic pathological feature recently included as a histological factor in the 9th Edition of the TNM Classification¹.
- Clinical significance of STAS according to **epidermal growth factor receptor (*EGFR*)** mutation status remains unclear.
- We aimed to elucidate differences in the clinical significance of STAS according to *EGFR* mutation status.

METHODS

Patients

312 patients with completely resected pathological stage I-IIIB lung adenocarcinoma between 2015 and 2022.

Methods

We investigated the association between clinicopathological features and STAS, and evaluated prognosis according to *EGFR* mutation status.

A flow diagram of patients

Pathological stage I-IIIB lung adenocarcinoma with complete resection (n = 789)

- History of neoadjuvant therapy (n=30)
- not available for data about STAS (n=227)
- not available for data about *EGFR* (n=213)
- pneumonectomy (n=7)

Eligible patients (n = 312)

- *EGFR*-mutant (n=165, 52.9%)
- *EGFR*-wild (n=147, 47.1%)

RESULTS

Table 1. Association between *EGFR* mutation status and clinicopathological features (n=312)

	Factor	<i>EGFR</i> -mutant (n=165)	<i>EGFR</i> -wild (n=147)	p value		Factor	<i>EGFR</i> -mutant (n=165)	<i>EGFR</i> -wild (n=147)	p value
Age	< 70	80 (53.3%)	70 (47.6%)	0.866	pI	-	137 (83.0%)	113 (76.9%)	0.174
	≥ 70	77 (46.7%)	77 (52.4%)			+	28 (17.0%)	34 (23.1%)	
Sex	man	65 (39.4%)	86 (58.5%)	<0.001	ly	-	137 (83.0%)	124 (84.4%)	0.752
	female	100 (60.6%)	61 (41.5%)			+	28 (17.0%)	23 (15.6%)	
Pathological Stage	I	122 (73.9%)	86 (58.5%)	0.004	v	-	150 (90.9%)	123 (83.7%)	0.054
	II-III	43 (26.1%)	61 (41.5%)			+	15 (9.1%)	24 (16.3%)	
Histological Grade	G1-2	136 (82.4%)	96 (65.3%)	<0.001	STAS	-	130 (78.8%)	100 (68.0%)	0.031
	G3	29 (17.6%)	51 (34.7%)			+	35 (21.2%)	47 (32.0%)	

Figure. Kaplan–Meier curves of recurrence-free survival (RFS) and overall survival (OS) according to STAS.

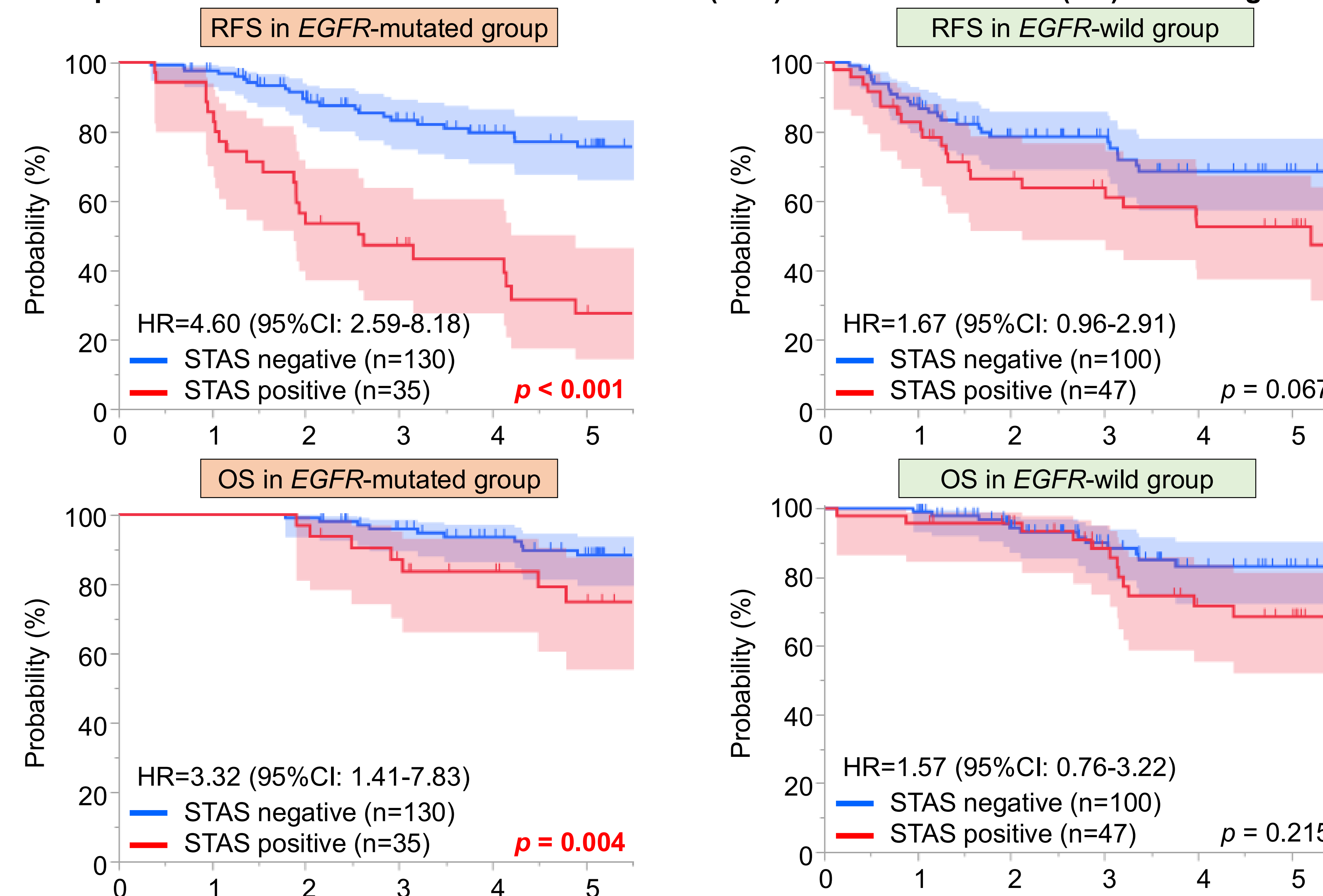


Table 3. Univariable and multivariable analyses of RFS in patients with *EGFR*-mutated and *EGFR*-wild group

Factors	<i>EGFR</i> -mutated				<i>EGFR</i> -wild			
	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
pStageII-III	5.97 (3.33-10.73)	<0.001	4.35 (2.36-8.02)	<0.001	3.39 (1.92-6.01)	<0.001	2.78 (1.55-4.99)	<0.001
Grade G3	4.46 (2.49-7.99)	<0.001	2.28 (1.23-4.22)	0.009	2.18 (1.26-3.78)	0.006		
pI +	2.23 (1.19-4.18)	0.012			2.82 (1.61-4.94)	<0.001	2.06 (1.15-3.70)	0.016
ly +	5.32 (2.93-9.65)	<0.001			4.00 (2.24-7.14)	<0.001	2.42 (1.30-4.49)	0.005
v +	2.44 (1.14-5.23)	0.022			3.00 (1.66-5.42)	<0.001		
STAS +	4.60 (2.59-8.18)	<0.001	2.90 (1.59-5.30)	<0.001	1.67 (0.96-2.91)	0.070		

Table 2. Association between *EGFR* mutation status and histological subtypes

Histological subtype	<i>EGFR</i> -mutated (n = 165)	<i>EGFR</i> -wild (n = 147)	p value
AIS/MIA	8 (4.8%)	5 (3.4%)	<0.001
Lepidic	26 (15.8%)	9 (6.1%)	
Acinar	106 (64.2%)	74 (50.3%)	
Papillary	14 (8.5%)	4 (2.7%)	
Micropapillary	5 (3.0%)	34 (2.7%)	
Solid	6 (3.7%)	30 (20.4%)	
Others	0 (0.0%)	21 (14.3%)	

Differences in histologic subtypes between *EGFR* mutated and wild group may have influenced the frequency of STAS.

DISCUSSION AND CONCLUSION

Key Findings

- STAS was more frequently identified in *EGFR*-wild type than *EGFR*-mutation.
- STAS was significantly associated with poor RFS and OS in *EGFR*-mutated group, but not in *EGFR*-wild.

Actionable Take Away Message

- STAS may have increased clinical relevance in patients with *EGFR*-mutation.

Future Direction for Research

- Future studies should investigate the biological mechanisms underlying the differential clinical significance of STAS in *EGFR*-mutant and *EGFR* wild-type lung adenocarcinoma, which may facilitate more personalized risk stratification and treatment strategies.

REFERENCES & ACKNOWLEDGEMENTS

1. Travis WD, et al. J Thorac Oncol 2024;19:1028–51.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.