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Spread through air spaces as a prognostic factor in resected non-small cell lung cancer

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ABSTRACT

Aims: To evaluate the prognostic impact of spread through air spaces (STAS) in patients with resected non-small cell lung cancer (NSCLC) and to investigate its association with clinicopathological features and survival outcomes.

Methods: A retrospective analysis was conducted on 207 patients with pathological stage IA–IIIA NSCLC who underwent curative-intent surgery between 2018 and 2024. STAS was defined as the presence of micropapillary clusters, solid nests, or single tumor cells within alveolar spaces beyond the main tumor. Patients were categorized as STAS-positive or STAS-negative. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan–Meier method. Univariate and multivariate Cox regression models were used to assess prognostic factors.

Results: STAS was identified in 57% of patients. STAS positivity was significantly associated with poor differentiation, a higher rate of lymphovascular invasion, and increased use of adjuvant chemotherapy. Median DFS was 29.9 months in STAS-positive patients but was not reached in STAS-negative patients ($p<0.001$). In multivariable analysis, STAS independently predicted shorter DFS (HR: 2.38; 95% CI: 1.34–4.23; $p=0.003$). No statistically significant association was found between STAS and OS ($p=0.079$).

Conclusion: STAS is an independent adverse prognostic factor for DFS in resected NSCLC. Its presence should be considered in prognostic evaluation and surgical planning, particularly in patients with early-stage disease.

Keywords: Non-small cell lung cancer, STAS, disease-free survival, prognostic factors, surgery

INTRODUCTION

In recent years, the implementation of low-dose computed tomography screening programs in some countries has led to a declining trend in lung cancer incidence and mortality. However, lung cancer remains the most frequently diagnosed malignancy and the leading cause of cancer-related death worldwide. According to GLOBOCAN 2022 estimates, there were 2.48 million new cases and 1.82 million deaths globally, reflecting the ongoing burden of this disease.[1] Despite improvements in early detection, non-small cell lung cancer (NSCLC) continues to exhibit aggressive biological behavior even in early-stage and operable disease. SEER data indicate that the 5-year recurrence rate after surgical resection for NSCLC ranges from approximately 30% to nearly 70%.[2] These findings underscore the need for robust prognostic stratification at the time of diagnosis, particularly in early-stage disease.

Several prognostic factors associated with unfavorable outcomes after surgical resection have been identified, including pleural invasion, lymphovascular invasion (LVI), poor tumor differentiation, wedge resection, and unknown lymph node status.[3] In this context, spread through air spaces (STAS) which is described by the World Health Organization (WHO) in 2015, initially in lung adenocarcinoma. Since then, STAS has garnered increasing attention for its potential prognostic significance in NSCLC.[4,5] STAS is defined as the presence of tumor cells within the adjacent alveolar parenchyma beyond the edge of the main tumor, detectable microscopically in lung cancer specimens. It has been reported in approximately 15% to 73% of surgically resected lung cancers and is associated with poor prognosis.[6-10] This adverse prognostic association has been consistently observed across all major histological subtypes of lung cancer studied, including adenocarcinoma, squamous cell carcinoma, small cell carcinoma and others.[11,12]

While many of the traditional prognostic factors reflect tumor burden or invasiveness, they may not fully capture

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microscopic patterns of tumor spread that directly influence the risk of recurrence. STAS represents a distinct pattern of tumor dissemination through alveolar spaces, independent of vascular or lymphatic spread.[13] Importantly, its presence has been associated with worse outcomes even among patients with otherwise favorable pathological features. These observations suggest that STAS may serve as an independent prognostic marker and a valuable criterion for informing surgical decisions, particularly when considering sublobar resections.[14,15] Accordingly, increasing efforts have been made to incorporate STAS into prognostic algorithms and clinical decision-making in resectable NSCLC.

Therefore, the aim of this study was to evaluate the prognostic significance of STAS in patients with resected NSCLC, and to investigate its association with clinicopathological factors and survival outcomes in a real-world, single-center cohort.

METHODS

Ethics

The study has been approved by the Scientific Researches Ethics Committee of Gülhane Training and Research Hospital (Date: 06.05.2025, Decision No: 2025-275). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This retrospective single-center study included 207 patients who underwent curative-intent surgical resection for pathological stage IA–IIIA NSCLC between 2018 and 2024 at Gülhane Training and Research Hospital. Eligible patients were selected based on the availability of pathological STAS assessment and complete clinical and follow-up data.

Demographic variables (age, sex), smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), tumor characteristics (histological subtype, differentiation, tumor size), pathological features (LVI, perineural invasion [PNI], visceral pleural invasion [VPI]), and molecular markers (PD-L1 expression, mutational status) were recorded. Radiological staging with positron emission tomography/computed tomography (PET/CT), type of surgical intervention (wedge resection, lobectomy), and lymph node evaluation status were also collected. Surgical approach and extent of resection were determined based on tumor size, location, and patient comorbidities. Of the total 207 patients, 9 underwent wedge resection and 2 underwent other forms of sublobar resection due to high comorbidity burden and/or small tumor size. The remaining patients were treated with lobectomy or pneumonectomy accompanied by systematic mediastinal and hilar lymph node sampling.

Prognostic outcomes included overall survival (OS) and disease-free survival (DFS). OS was defined as the time from the date of surgery to death from any cause, and DFS as the time from surgery to recurrence or death. The primary objective was to evaluate the prognostic impact of STAS on survival outcomes.

Histopathological Assessment

Histopathological evaluation was performed on resection specimens obtained during definitive surgery. STAS assessment was performed exclusively on resection specimens; no frozen sections or preoperative biopsies were used. All specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin, and processed according to routine histological procedures. Four-micron thick sections were stained with hematoxylin and eosin (H&E) for microscopic examination.

STAS was defined in accordance with the 2015 WHO classification of lung tumors as the presence of tumor cells either as micropapillary clusters, solid nests, or single tumor cells within alveolar spaces beyond the edge of the main tumor. To minimize misinterpretation due to histological artifacts, particular attention was paid to exclude free-floating cell strips or fragmented clusters lacking alveolar attachment, as these are often considered artifacts from specimen handling rather than true STAS. All histopathological assessments were performed by an experienced thoracic pathologist as part of routine diagnostic practice at our institution. A second, independent pathology review was not conducted for this retrospective study. Tumor histological subtype, grade, and presence of lymphovascular or pleural invasion were also assessed and documented.

Statistical Analysis

Clinicopathological variables were compared between STAS-positive and STAS-negative groups using Pearson's Chi-squared test or Fisher's exact test, as appropriate. Descriptive statistics were presented as numbers and percentages for categorical variables.

OS and DFS were estimated using the Kaplan–Meier method, and survival differences between STAS subgroups were assessed using the log-rank test. The median follow-up time was calculated using the reverse Kaplan–Meier method. Univariate Cox proportional hazards regression was used to identify factors associated with OS and DFS. Variables with a p-value <0.05 in the univariate analysis were included in the multivariate Cox regression model to identify independent prognostic factors. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

RESULTS

Clinicopathological Characteristics of the Patients

The clinicopathological characteristics of the 207 patients are summarized in **Table 1**. The median age was 64 years (min-max: 39–82), and 78.7% were younger than 70 years. Most patients were male (78.3%, n=162). Regarding smoking history, 82.2% were active or former smokers, and 17.8% had never smoked. STAS positivity was identified in 118 patients (57%), whereas 89 patients (43%) were STAS-negative.

Table 1. Demographic and clinicopathological parameters according to STAS status

Variables	All patients n=207	STAS (+) n=118	STAS (-) n=89	p value
Age, median (min-max)	64 (39-82)	64 (41-82)	62 (39-81)	0.37
<70 years, n (%)	163 (78.7%)	91 (77.1%)	72 (80.9%)	0.61
≥70 years, n (%)	44 (21.3%)	27 (22.9%)	17 (19.1%)	
Sex, n (%)				
Female	45 (21.7%)	20 (16.9%)	25 (28.1%)	0.06
Male	162 (78.3%)	98 (83.1%)	64 (71.9%)	
Smoking status, n (%)	35 (17.8%)	19 (17%)	16 (18.8%)	
Never smoker	162 (82.2%)	93 (83%)	69 (81.2%)	0.86
Active/former-smoker				
Type of surgery, n (%)				
Wedge	11 (5.3%)	3 (2.5%)	8 (9%)	
Lobectomy	185 (89.4%)	111 (94.1%)	74 (83.1%)	0.038
Pneumonectomy	11 (5.3%)	4 (3.4%)	7 (7.9)	
TNM stage, n (%)				
1A	74 (35.7%)	31 (26.3%)	43 (48.3%)	
1B	48 (23.2%)	24 (20.3%)	24 (27%)	
2A	13 (6.3%)	10 (8.5%)	3 (3.4%)	0.001
2B	34 (16.4%)	2.5 (2.2%)	9 (10.1%)	
3A	38 (18.4%)	28 (23.7%)	10 (11.2%)	
Pathological type, n (%)				
Adenocarcinoma	126 (60.9%)	67 (56.8%)	59 (66.3%)	
SqCC	70 (33.8%)	46 (39%)	24 (27%)	0.17
LC-NEC	11 (5.3%)	5 (4.2%)	6 (6.7%)	
Histological grading, n (%)				
Good	21 (10.9%)	7 (6.4%)	14 (17.1%)	
Moderate	124 (64.6%)	69 (62.7%)	55 (67.1%)	0.009
Poor	47 (24.5%)	34 (30.9%)	13 (15.9%)	
LVI, n (%)				
Presence	85 (41.1%)	56 (47.5%)	29 (32.6%)	0.033
Absence	122 (58.9%)	62 (52.5%)	60 (67.4%)	
VPI, n (%)				
Presence	61 (29.5%)	38 (32.2)	23 (25.8%)	0.358
Absence	146 (70.5%)	80 (67.8%)	66 (74.2%)	
Adenocarcinoma subtypes, n (%)	126 (100%)			
Lepidic	68 (54%)	30 (44.8%)	38 (64.4%)	0.032
Acinar	90 (71.4%)	46 (68.7%)	44 (74.6%)	0.554
Solid	54 (42.9%)	33 (49.3%)	21 (35.6%)	0.122
Papillary	47 (39.3%)	24 (35.8%)	23 (39%)	0.854
Micropapillary	19 (15.1%)	13 (19.4%)	6 (10.2%)	0.212
PDL1, n (%)	78 (100%)			
<1	53 (67.9%)	34 (67.3%)	16 (69.6%)	0.843
≥1	25 (32.1%)	18 (32.7%)	7 (30.4%)	
Mutational status, n (%)	76 (100%)			
EGFR	8 (10.5%)	5 (9.6%)	3 (12.5%)	
KRAS	5 (6.6%)	4 (7.7%)	1 (4.2%)	0.793
None	63 (82.9%)	43 (82.7%)	20 (83.3%)	
Adjuvant CT, n (%)	141(68.1%)	88 (74.6%)	53 (59.6%)	
Presence	66 (31.9%)	30 (25.4%)	36 (40.4%)	0.024
Absence				
Progression	81 (39.1%)	62 (52.5%)	19 (21.3%)	<0.001
Exitus	49 (23.7%)	33 (28%)	16 (18%)	0.102

STAS: Spread through air spaces, LVI: Lymphovascular invasion, VPI: Visceral pleural invasion, DFS: Disease-free survival, OS: Overall survival, CT: Chemotherapy, EGFR: Epidermal growth factor receptor; KRAS: Kirsten rat sarcoma virus, PD-L1: Programmed death ligand 1, SqCC: Squamous cell carcinoma, LC-NEC: Large cell neuroendocrine carcinoma, TNM: Tumor-node-metastasis (staging system).
Note: Percentages in Table 1 are calculated column-wise. Chi-square test was used for comparisons between STAS-positive and STAS-negative groups.

Lobectomy was the most common surgical approach (89.4%, n=185). Pathological staging revealed stage IA in 35.7% of patients, IB in 23.2%, IIA in 6.3%, IIB in 16.4%, and IIIA in 18.4%. Stage IA was significantly more common among STAS-negative patients (48.3% vs. 26.3%, p=0.001).

Histologically, 60.9% of tumors were adenocarcinomas (n=126), 33.8% were squamous cell carcinomas (n=70), and 5.3% were other subtypes, including large cell neuroendocrine carcinoma and atypical carcinoid tumors (p=0.17). In terms of differentiation, 10.9% were well-differentiated, 64.6% were moderately differentiated, and 24.5% were poorly differentiated. Poor differentiation was significantly more common in the STAS-positive group (30.9% vs. 15.9%, p=0.009). LVI was observed in 41.1% (n=85) of cases, with a higher prevalence in STAS-positive patients (47.5% vs. 32.6%, p=0.033). VPI was observed in 29.5% of patients, with no significant difference between STAS groups (p=0.358).

Molecular status (EGFR, ALK, ROS1, KRAS) was available for 76 patients (36.7%), and PD-L1 expression was assessed in 78 patients (37.7%). Among those tested, EGFR mutations were detected in 8 patients (10.5%) and KRAS mutations in 5 patients (6.6%). All patients tested for ALK and ROS1 rearrangements were negative. PD-L1 expression of ≥1% was observed in 25 patients (32.1%). The distribution of these

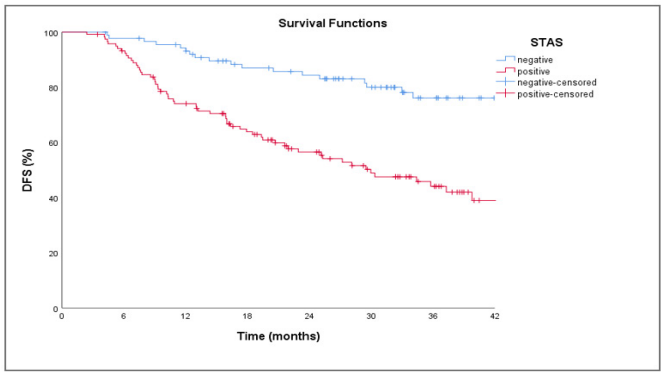
molecular alterations did not significantly differ between STAS-positive and STAS-negative groups (p>0.05 for all comparisons).

Adjuvant chemotherapy was administered to 68.1% of patients and was significantly more common in the STAS-positive group (74.6% vs. 59.6%, p=0.024). No patients received induction therapy before surgery.

Impact of STAS on Survival Outcomes

The median follow-up duration was 36.5 months. During this period, the estimated median DFS was 51.7 months, and the median OS was 90.6 months. However, CIs could not be calculated because of the high proportion of censored cases.

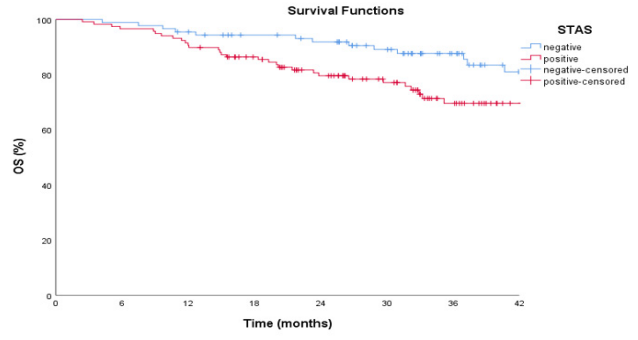
STAS-positive patients had significantly worse survival outcomes. The median DFS in the STAS-positive group was 29.9 months (95% CI: 20.6–39.4), while it was not reached in the STAS-negative group (p<0.001). Similarly, the median OS was 62.3 months (95% CI: 35.2–89.4) in STAS-positive patients and was not reached in the STAS-negative group (p=0.017). Kaplan-Meier survival curves for DFS and OS according to STAS status are presented in **Figure 1, 2**.



No. at risk

Months	0	6	12	18	24	30	36	42
STAS-negative	88	85	79	73	67	62	57	51
STAS-positive	117	114	107	101	95	89	83	78

Figure 1. Kaplan-Meier curves for disease-free survival (DFS) according to STAS status. Median DFS was 29.9 months in STAS-positive patients and not reached in STAS-negative patients (log-rank p<0.001).
STAS: Spread through air spaces



No. at risk

Months	0	6	12	18	24	30	36	42
STAS-negative	88	87	83	80	76	70	63	57
STAS-positive	117	115	112	108	104	98	93	87

Figure 2. Kaplan-Meier curves for overall survival (OS) according to STAS status. STAS-positive patients had significantly shorter median OS compared to STAS-negative patients (62.3 vs. not reached; p=0.017).
STAS: Spread through air spaces

In univariable analysis, in addition to STAS positivity, several clinicopathological variables were significantly associated with shorter DFS. Poor tumor differentiation (HR: 2.36; 95% CI: 1.56-3.58; p<0.001), presence of LVI (HR: 1.84; 95% CI: 1.19-2.86; p=0.006) and VPI (HR: 1.90; 95% CI: 1.21-2.97; p=0.005) were also significantly associated with worse DFS. Patients who received adjuvant chemotherapy had shorter DFS compared to those who did not (HR: 1.87; 95% CI: 1.12-3.14; p=0.016). In contrast, age, sex, smoking status, type of surgery, and histologic subtype were not significantly associated with DFS. Three-year DFS rates differed significantly according to TNM stage, with stage IA showing the most favorable rate (73.6%). **Table 2** summarizes the univariable analyses for DFS and OS.

In the multivariable Cox regression model, STAS positivity remained an independent predictor of disease recurrence (HR: 2.38; 95% CI: 1.34–4.23; p=0.003). VPI was also significantly associated with shorter DFS (HR: 1.79; 95% CI: 1.03–3.10; p=0.038), as was poor differentiation (HR: 3.53; 95% CI: 1.17–10.62; p=0.025). TNM stage, LVI, and adjuvant chemotherapy were not statistically significant in this model.

In the multivariable model for OS, age ≥70 years was independently associated with poorer survival (HR: 2.50; 95% CI: 1.27–4.92; p=0.008). Although STAS positivity (HR: 1.86; 95% CI: 0.93–3.72; p=0.079) and poor differentiation (HR: 3.05; 95% CI: 0.84–11.03; p=0.090) demonstrated a trend toward poorer OS, these did not reach statistical significance. Other variables, including TNM stage, LVI, and adjuvant chemotherapy, were not independently associated with OS. Multivariable Cox regression analyses for DFS and OS are presented in **Table 3**.

DISCUSSION

In this retrospective cohort study, we demonstrated that the presence of STAS was significantly associated with several adverse clinicopathological features, including higher pathological stage, poor tumor differentiation, and LVI. In multivariable analyses, STAS emerged as an independent predictor of DFS (HR: 2.38; 95% CI: 1.34–4.23; p=0.003). These findings suggest that STAS is not merely a histopathological observation but may reflect a more aggressive tumor biology, contributing to an increased risk of recurrence even in early-stage disease.

The incidence of STAS in our cohort was 57%, which is within the higher range reported in the literature. Previous studies, such as those by Toyokawa et al.[10] and Gutierrez-Sainz et al.,[16] reported STAS positivity rates of 71.2% and 73%, respectively. These elevated rates were largely attributed to the inclusion of patients with more advanced disease stages (stage II and III) in their cohorts. Similarly, our study also revealed a significant association between STAS positivity and higher pathological stage; stage IA disease was notably more frequent among STAS-negative patients (48.3% vs. 26.3%, p=0.001). These results support earlier findings that STAS is closely linked to tumor aggressiveness and may reflect more advanced tumor biology.

Table 2. Univariable analysis for DFS and OS

		Univariable for DFS		Univariable for OS	
Variables	**3 year DFS (%)**	**HR (95% CI)**	**p value**	**HR**	**p value**
<70 years	59.2	Reference	0.509	Reference	0.003
>70 years	54.4	1.19(0.70-2.04)		2.48 (1.37-4.50)	
Female	62.6	Reference	0.296	Reference	0.358
Male	56.9	1.34 (0.76-2.36)		1.42 (0.66-3.05)	
Never smoker	51.2	Reference	0.800	Reference	0.720
Active/former smoker	58.3	1.08 (0.59-1.96)		1.15 (0.51-2.58)	
Wedge resection	60.0	Reference	0.815	Reference	0.140
Lobectomy	58.8	0.85 (0.31-2.35)	0.766	0.61 (0.28-1.71)	0.347
Pneumonectomy	48.5	1.12 (0.30-4.19)	0.863	1.45 (0.39-5.45)	0.575
TNM stage					
1A	73.6	Reference	<0.001	Reference	0.003
1B	69.7	0.97 (0.48-1.96)	0.945	0.52 (0.18-1.48)	0.226
2A	41.0	2.73 (1.15-6.48)	0.022	3.78 (1.42-10.04)	0.008
2B	34.2	2.76 (1.47-5.18)	0.002	2.00 (0.89-4.46)	0.091
3A	40.9	3.00 (1.60-5.51)	<0.001	2.45 (1.13-5.31)	0.023
LVI					
Absent	68	Reference	0.006	Reference	0.030
Present	44.6	1.84 (1.19-2.86)		1.87 (1.06-3.31)	
VPI					
Absent	65.3	Reference	0.005	Reference	0.144
Present	42.3	1.90 (1.21-2.97)		1.54 (0.86-2.78)	
STAS					
Absent	76.1	Reference	<0.001	Reference	0.019
Present	44.1	3.60 (2.13-6.06)		2.10 (1.13-3.90)	
Differantiation					
Good	77.0	Reference	<0.001	Reference	0.030
Intermediate	63.0	2.13 (0.76-5.98)	0.147	1.36 (0.41-4.53)	0.613
Poor	38.9	5.19(1.80-14.95)	0.002	3.53 (0.88-10.66)	0.077
Histological subtype					
Adenocancer	58.5	Reference	0.693	Reference	0.350
Squamous cell cancer	58.9	0.86 (0.53-6.40)	0.562	1.66 (0.90-3.03)	0.099
Others	50.9	1.27 (0.50-3.21)	0.601	3.30 (1.24-8.77)	0.016
Adjuvant CT					
Absent	72.7	Reference	0.016	Reference	0.020
Present	51.5	1.87 (1.12-3.14)		2.36 (1.14-4.89)	

STAS: Spread through air spaces, LVI: Lymphovascular invasion, VPI: Visceral pleural invasion, DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, CT: Chemotherapy, TNM: Tumor-node-metastasis (staging system)

Table 3. Multivariable Cox regression analysis for DFS and OS

	DFS		OS	
Variables	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age <70 vs >70			2.50 (1.27-4.92)	0.008
TNM stage				
1A vs	Reference	0.337	Reference	0.106
1B	0.54 (0.22-1.36)	0.198	0.25 (0.07-0.89)	0.032
2A	0.99 (0.35-2.79)	0.994	1.29 (0.40-4.09)	0.666
2B	1.08 (0.41-2.88)	0.867	0.59 (0.19-1.81)	0.364
3A	1.26 (0.49-3.20)	0.625	0.98 (0.34-2.77)	0.976
LVI (absent vs present)	1.49 (0.86-2.56)	0.148	1.79 (0.89-3.58)	0.100
VPI (absent vs present)	1.78 (1.03-3.10)	0.038		
STAS (absent vs present)	2.38 (1.34-4.23)	0.003	1.85 (0.93-3.71)	0.079
Differantiation	Reference	0.005	Reference	0.036
Good vs intermediate	1.58 (0.55-4.50)	0.389	1.30 (0.38-4.41)	0.667
Good vs poor	3.53 (1.17-10.6)	0.025	3.04 (0.84-11.03)	0.090
Adjuvant CT	1.08 (0.49-2.35)	0.844	2.20 (0.81-5.92)	0.119

STAS: Spread through air spaces, LVI: Lymphovascular invasion, VPI: Visceral pleural invasion, DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, CT: Chemotherapy, TNM: Tumor-node-metastasis (staging system).

In addition to pathological stage, STAS was also associated with tumor histologic subtype and differentiation.[17,18] In our study, STAS was more frequently observed in poorly differentiated tumors, further supporting its link to aggressive tumor behavior. Among adenocarcinoma subtypes, the absence of a lepidic component was associated with the presence of STAS. Consistent with our findings, studies by Xie et al.[19] and Cao et al.[20] have also demonstrated that the solid growth pattern is significantly correlated with STAS positivity.

The prognostic importance of STAS is increasingly recognized in the literature. In a recent study by Chen et

al.[21] focusing on stage IA lung adenocarcinoma ≤2 cm, STAS was found in 43.4% of cases, and its association with adverse pathological features, including poor differentiation and LVI, was confirmed. Importantly, STAS remained an independent prognostic factor for OS in multivariate analysis. Similarly, another study showed that STAS was associated with worse 5-year DFS and OS in stage IB (T2aN0) NSCLC patients, emphasizing its impact even in early stage disease.[6] A large-scale analysis by the International Association for the Study of Lung Cancer (IASLC) included 4.061 resected NSCLC cases and found STAS in 22.9% of tumors. In this study, STAS was independently associated with both DFS and OS, regardless of disease stage. Based on these data, the authors suggested that STAS should be included in the 9th TNM classification, along with factors such as visceral pleural and LVI.[5] According to our findings, STAS is an independent prognostic marker for DFS. While a trend toward worse OS was observed in STAS-positive patients, this association did not reach statistical significance in our multivariate analysis (HR: 1.86; 95% CI: 0.93–3.72; p=0.079). This may be explained by the relatively low number of events and the limited follow-up duration in our cohort, both of which could have reduced the statistical power to detect a significant difference. With longer follow-up and larger patient numbers, the prognostic impact of STAS on OS may become more evident.

Our study did not find a significant association between STAS and molecular markers such as PD-L1 expression or driver mutations. However, this should be interpreted cautiously, as molecular testing was unavailable in approximately two-thirds of patients. This reflects the national healthcare context in Turkiye during the study period, when molecular testing was not routinely performed for early-stage NSCLC due to lack of reimbursement and limited access to targeted therapies and immunotherapies. Consequently, molecular profiling was often limited to patients with recurrence, thereby reducing the ability to explore correlations between STAS and specific molecular alterations in the overall cohort.

The relationship between STAS and molecular alterations remains controversial in the literature. Lee et al.[17] and Gutierrez-Sainz et al.[16] found that EGFR mutations were less common in STAS-positive tumors, suggesting a potential inverse correlation. In contrast, Tian et al.[22] reported that STAS was more frequently observed in EGFR-mutant tumors and, demonstrated a significant association between ALK alterations and STAS positivity. Further insights were gained from a recent large-scale genomic profiling study by Ye et al.[23] who analysed 442 resected lung adenocarcinomas using next-generation sequencing. They found that EGFR mutations were significantly less frequent in STAS-positive tumors (52.5% vs. 69.7%, p<0.001), while TP53 mutations and ALK rearrangements were enriched in the STAS-positive group. Taken together, these conflicting and evolving data underline the complexity of STAS pathogenesis and highlight the need for further large-scale studies with standardized molecular profiling to clarify these associations.

In our study, lobectomy was more commonly performed in STAS-positive patients. The number of patients who underwent sublobar resection in our cohort was limited, which restricts our ability to draw definitive conclusions regarding the impact of STAS positivity on surgical outcomes in this subgroup. Several studies have reported that patients with STAS-positive tumors who undergo sublobar resections such as wedge resection or segmentectomy have higher recurrence rates and worse disease-free and OS compared to those who undergo lobectomy.[24,25] However, this association remains controversial. Kagimoto et al.[26] found that segmentectomy provided comparable oncologic outcomes to lobectomy in patients with stage IA lung adenocarcinoma with STAS, without increasing the risk of locoregional recurrence. Furthermore, some investigators have suggested that adjuvant therapy may be warranted in STAS-positive patients undergoing sublobar resections, particularly in early-stage disease, to mitigate the risk of recurrence.[27] Overall, these results highlight the importance of considering STAS as both a prognostic biomarker and a factor that may influence surgical decision-making; however, these conclusions should be interpreted with caution and require validation in larger studies.

Limitations

This study has several limitations. First, it was a retrospective, single-center analysis, which may have introduced selection bias and limited the generalizability of the results. Second, although the cohort size was moderate, the number of events and duration of follow-up may have been insufficient to detect statistically significant differences in OS. Third, molecular testing was not performed in a substantial proportion of patients, and as a result, our ability to comprehensively evaluate the association between STAS and specific molecular alterations was limited.

CONCLUSION

As a result, our findings confirm that the presence of STAS is significantly associated with adverse pathological features and independently predicts DFS in resected NSCLC. These results highlight the potential clinical utility of STAS as a prognostic biomarker particularly in early-stage disease. Future prospective studies with longer follow-up and comprehensive molecular profiling are needed to validate and expand these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study has been approved by the Scientific Researches Ethics Committee of Gülhane Training and Research Hospital (Date: 06.05.2025, Decision No: 2025-275).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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