ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer (IASLC) Staging Project for Lung Cancer: Recommendation to Introduce Spread Through Air Spaces as a Histologic Descriptor in the Ninth Edition of the TNM Classification of Lung Cancer. Analysis of 4061 Pathologic Stage I NSCLC

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2024.03.015

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Received 8 December 2023; revised 6 March 2024; accepted 13 March 2024
Available online - 18 March 2024

ABSTRACT

Introduction: Spread through air spaces (STAS) consists of lung cancer tumor cells that are identified beyond the edge of the main tumor in the surrounding alveolar parenchyma. It has been reported by meta-analyses to be an independent prognostic factor in the major histologic types of lung cancer, but its role in lung cancer staging is not established.

Methods: To assess the clinical importance of STAS in lung cancer staging, we evaluated 4061 surgically resected pathologic stage I R0 NSCLC collected from around the world in the International Association for the Study of Lung Cancer database. We focused on whether STAS could be a useful additional histologic descriptor to supplement the existing ones of visceral pleural invasion (VPI) and lymphovascular invasion (LVI).

Results: STAS was found in 930 of 4061 of the pathologic stage I NSCLC (22.9%). Patients with tumors exhibiting STAS had a significantly worse recurrence-free and overall survival in both univariate and multivariable analyses involving cohorts consisting of all NSCLC, specific histologic types (adenocarcinoma and other NSCLC), and extent of resection (lobar and sublobar). Interestingly, STAS was independent of VPI in all of these analyses.

Conclusions: These data support our recommendation to include STAS as a histologic descriptor for the Ninth Edition of the TNM Classification of Lung Cancer. Hopefully, gathering these data in the coming years will facilitate a thorough analysis to better understand the relative impact of STAS, LVI, and VPI on lung cancer staging for the Tenth Edition TNM Stage Classification.

Keywords: Lung cancer; Stage classification; Spread through air spaces; Visceral pleural invasion; Histologic descriptor; Lymphovascular invasion

Introduction

Spread through air spaces (STAS) is a lesion where lung cancer tumor cells are identified microscopically beyond the edge of the main tumor in the adjacent alveolar parenchyma.[1–3] It has been reported in 20% to 40% of surgically resected lung cancers and is associated with poor prognosis as reported in meta-analyses of published reports from institutions worldwide.[4–9] This association with worse survival has been found in all major histologic types of lung cancer studied, including adenocarcinoma,[1,10–12] squamous cell carcinoma,[13] small cell carcinoma,[14] large cell neuroendocrine carcinoma,[14], atypical carcinoid,[14] and pleomorphic carcinoma.[6,15]

Multiple investigators have suggested that STAS be incorporated in the TNM stage classification of lung cancer in a variety of ways such as tumor size, residual tumor (R) status, or as a histologic descriptor that could upstage T1 lung cancers to T2a categories similar to visceral pleural invasion (VPI).[10,12,16–20] Therefore, the role of STAS in lung cancer stage classification was investigated by the Staging and Prognostic Factors Committee (SPFC) of the International Association for the Study of Lung Cancer (IASLC) in preparing the ninth edition of the TNM classification. We report herein the results of analyses for STAS in completely resected (R0) stage I (T1/T2a N0M0) NSCLC in the IASLC ninth edition staging database. The focus of this analysis was to investigate whether STAS could be a useful additional histologic descriptor to supplement the existing ones recognized by both the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) of VPI, lymphatic/vascular invasion (LVI), and perineural invasion (Pn).[21–23] It was not a goal of this paper to propose that STAS be used to modify overall stage groupings.

Methods

STAS was analyzed for cases diagnosed during the time period of 2016 to 2019, because it was first defined in 2015. All cases from the IASLC database were included if they had the following: pathologic diagnosis of NSCLC, histologic type, survival time, overall survival (OS) and recurrence-free survival (RFS), surgical resection, and known pathologic stage I N0M0R0 status.[24] Data regarding the presence or absence of STAS were available in 4061 resected NSCLC including 2934 pathologic (p)T1 (631 pT1a, 1,523 pT1b, 780 pT1c) and 1127 pT2a, N0M0R0 resected NSCLCs. OS and RFS data were available in all patients. Patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, and

prior history of neoadjuvant therapy were excluded. Neuroendocrine tumors (carcinoids, large cell neuroendocrine carcinoma, and small cell carcinoma) are the subject of a separate analysis. Cases in which STAS was not evaluated were excluded. If either lymphatic or vascular invasion were reported, then LVI was recorded as a positive result[21,25]; if both reported no invasion, then LVI was recorded as a negative result. Data on Pn were insufficient for analysis. Follow-up time for patients had a range of 0.01 to 6.46 years with a median follow-up for RFS of 3.20 years (95% confidence interval [CI]: 3.10–3.23) and 3.14 years (95% CI: 3.10–3.20) for OS. No molecular data were available for this analysis.

Grading was provided by the contributing institution according to the Grades 1, 2, 3, and 4 recommended by the UICC and AJCC.[23,26] The IASLC grading system for nonmucinous lung adenocarcinomas could not be used because it was first reported in 2020 and the data collection was closed for lung cancers diagnosed in 2019, one year before.[27] As explained in the adenocarcinoma results section, predominant histologic subtype was not used for grading. Using the cases where predominant histologic subtype was available for nonmucinous lung adenocarcinomas, multivariate analyses were performed to determine whether STAS remained independent of histologic subtypes, particularly the poor prognostic subtypes of solid and micropapillary patterns. The not otherwise specified (NOS) category was proposed in the data elements for the Ninth Edition IASLC lung cancer database for adenocarcinomas that did not fall into one of the major histologic subtypes. There is no established grading system for squamous cell carcinoma.[28]

Contributions of cases came from Asia (China, South Korea, Taiwan, India, and Turkey) and Australia, North America (United States and Canada), Europe (Italy, Spain, Belgium, and Germany), South America (Brazil, Argentina, and Chile), and Africa (Morocco).

The frequency of STAS was compared by sex, age ($<$65 versus $\geq$65 y), surgical procedure, histologic type, tumor grade, LVI, tumor size ($\leq$3.0 versus $>$3.0 cm), VPI, and other T2 invasion descriptors which correspond to central tumors (involves main bronchus, associated with atelectasis or obstructive pneumonitis that extends to the hilar region either involving part of or the entire lung).

The end points analyzed were RFS, which was measured from time of surgery to disease recurrence or death from any cause, and OS, which was measured from date of surgery to death from any cause. Univariate and multivariable analysis was performed using Cox proportional hazards models. All multivariable models were adjusted for STAS (present versus absent), and then stepwise selection was used to adjust for other factors with an F statistical significance level of 0.1 for entry and a level of 0.05 to remain in the model. A partial likelihood ratio test was used to identify significant two-way interaction terms maintained in the multivariable model. Survival curves for patients with pathologic stage I (pT1/pT2aN0M0R0) tumors were generated by a Kaplan-Meier estimator with a log-rank test comparing survival based on the presence or absence of STAS. These analyses were performed in the following patient groups: all NSCLC, according to extent of surgical resection (lobar—lobectomy or bilobectomy; sublobar—wedge or segmentectomy), and according to histologic type (adenocarcinoma or "other NSCLC" including squamous cell carcinoma, adenosquamous carcinoma or large cell carcinoma). All survival and regression analyses were performed using SAS 9.4 (SAS Institute).

Results

STAS Frequency and Associated Clinical-Pathologic Characteristics

The frequency of STAS was highest in North America (46.2%), followed by Europe (29.4%), rest of the world (14.2%), and Asia (7%) (Supplementary Table 1). In the countries reporting STAS data in more than 50 lung cancers, the frequency was highest in Germany (56.4%), followed by USA (48.1%), Canada (43%), Turkey (36.7%), Spain (16.4%), and Taiwan (12.8%), and it was the lowest in Italy (1.4%) (Supplementary Table 2).

STAS was found in 930 of 4061 of the stage pI NSCLC (22.9%) (Table 1). STAS occurred significantly more frequently in older patients ($\geq$65 y) ($p < 0.0001$), in sublobar compared with lobar resections ($p = 0.0018$), in adenocarcinoma (838 of 3543, 23.7%) (Supplementary Fig. 1), adenosquamous carcinoma, or large cell carcinoma (13 of 49, 26.5%) compared with squamous cell carcinoma (79 of 469; 16.8%) ($p = 0.0036$), higher grade (3 or 4 versus 1 or 2) ($p < 0.0001$), LVI ($p < 0.0001$), VPI ($p < 0.0001$), and larger tumor size (both categorical $>/\leq$3.0 cm; $p = 0.0002$ and as a continuous variable, $p = 0.0002$) (Table 1). STAS was found less often in tumors with other T2 descriptors consisting of central bronchial tumors, although this was not significant ($p = 0.2249$). Also, STAS was not associated with sex ($p = 0.7892$).

STAS was found in increasing amounts according to pT category with 13% in pT1a, 22.4% in pT1b, 25.5% in pT1c, and 27.3% in pT2a tumors ($p < 0.0001$).

Prognostic Impact of STAS

All Patients With NSCLC. Among patients with stage pI NSCLC, RFS by Kaplan-Meier analysis revealed 91% 3-year survival without STAS compared with 80% with STAS (Fig. 1*A*) ($p < 0.001$) and 3-year OS of 95% without STAS compared with 88% with STAS (Fig. 1*B*) ($p < 0.001$).

Table 1. Distribution of STAS According to Clinicopathologic Characteristics

Patient/Tumor Characteristic	Total[b] (N = 4061)	STAS[a] Present (N = 930)	STAS[a] Absent (N = 3131)	*p* Value[c]
Sex, n (%)				0.7892
Female	2260 (55.7)	514 (22.7)	1746 (77.3)	
Male	1801 (44.3)	416 (23.1)	1385 (76.9)	
Age (y), n (%)				<0.0001
≥65	1911 (47.1)	564 (29.5)	1347 (70.5)	
<65	2150 (52.9)	366 (17.0)	1784 (83.0)	
Surgical procedure, n (%)				0.0018
Lobectomy	3177 (78.2)	693 (21.8)	2484 (78.2)	
Segmentectomy or wedge	884 (21.8)	237 (26.8)	647 (73.2)	
Histologic type, n (%)				0.0036
Adenocarcinoma	3543 (87.2)	838 (23.7)	2705 (76.3)	
Squamous	469 (11.5)	79 (16.8)	390 (83.2)	
Adenosquamous or large cell	49 (1.2)	13 (26.5)	36 (73.5)	
Tumor grade				<0.0001
1 or 2	2908 (77.0%)	598 (20.6%)	2310 (79.4%)	
3 or 4	870 (23.0%)	302 (34.7%)	568 (65.3%)	
Missing	283	30	253	
Lymphovascular invasion				<0.0001
No invasion	3524 (87.4%)	635 (18.0%)	2889 (82.0%)	
Invasion	508 (12.6%)	290 (57.1%)	218 (42.9%)	
Missing	29	5	24	
Visceral pleural invasion				<0.0001
Invasion	746 (18.4%)	211 (28.3%)	535 (71.7%)	
No invasion	3312 (81.6%)	716 (21.6%)	2596 (78.4%)	
Missing	3	3	0	
Central T2 invasion, n (%)				0.2249
Invasion	71 (1.7)	12 (16.9)	59 (83.1)	
No invasion	3990 (98.3)	918 (23.0)	3072 (77.0)	
Categorical tumor size, n (%)				0.0010
>3 cm	506 (12.5)	145 (28.7)	361 (71.3)	
≤3 cm	3555 (87.5)	785 (22.1)	2770 (77.9)	
Tumor size				0.0002[d]
N	4061	930	3131	
Mean (SD)	2.0 (0.88)	2.1 (0.88)	1.9 (0.88)	
Median (range)	1.8 (0.2-4.0)	1.9 (0.3-4.0)	1.8 (0.2-4.0)	

Note: Cohort includes all patients undergoing R0 resection for pI NSCLC with known STAS status.
[a]% values are row percentages.
[b]% values are column percentage for the subheading.
[c]*p* value for proportion with/without STAS within subcategory, chi-square *p* value (unless otherwise indicated).
[d]Kruskal-Wallis *p* value.
STAS, spread through air spaces.

To address potential confounders, a multivariable analysis was performed. STAS remained significantly associated with poor prognosis by univariate ($p < 0.001$) and multivariable ($p < 0.001$) analyses for both OS and RFS after adjusting for multiple factors including age, sex, histologic type (adenocarcinoma versus other histologic types), histologic grade, LVI, tumor size, VPI, and extent of resection (sublobar versus lobectomy) (Tables 2 and 3). Of note, an interaction between extent of resection and LVI was detected in the RFS, but not OS models, where extent of resection was significantly associated with RFS among patients with LVI, but not among patients without LVI. Nevertheless, STAS remained associated with RFS after accounting for this interaction. VPI remained independent in the multivariable analysis for RFS (Table 2) but not for OS (Table 3).

Histologic Type

Adenocarcinomas. STAS was significantly associated with adenocarcinoma histologic subtype (increasing percentages in both pT1/pT2a from lepidic [7.8%/7.2%], invasive mucinous adenocarcinoma or not

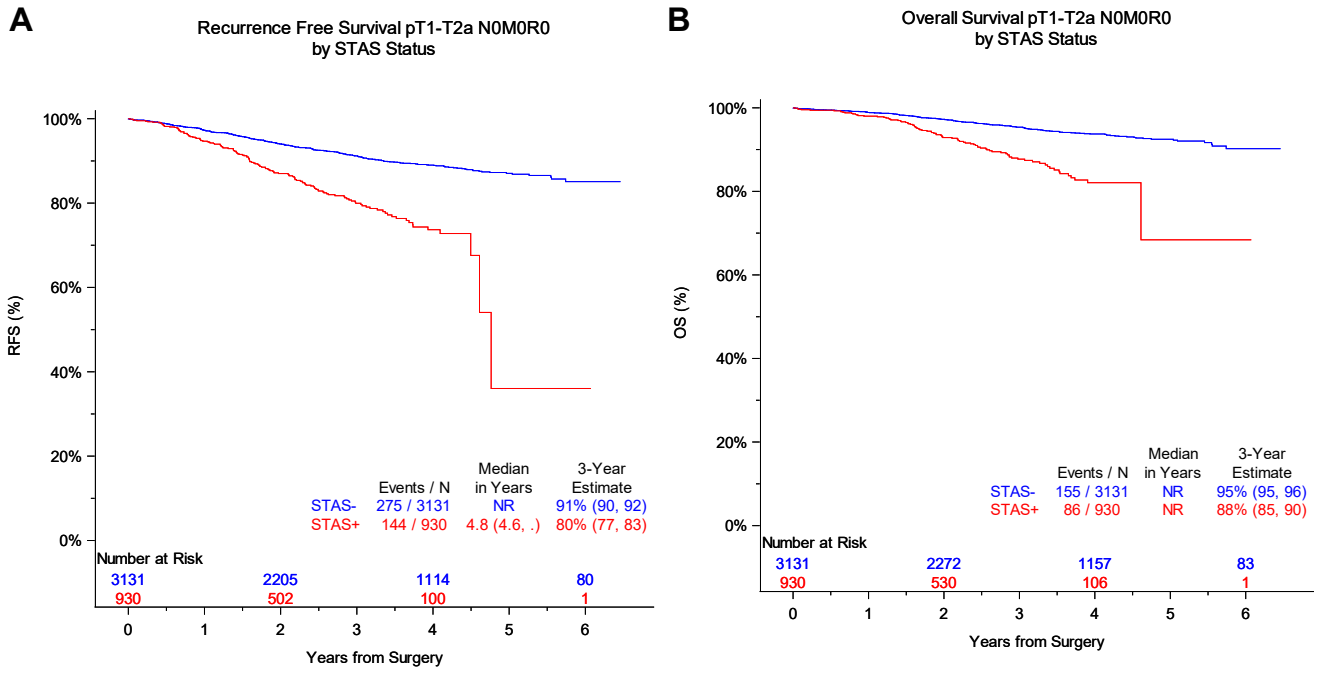

Figure 1. (*A*) Recurrence-free survival is significantly reduced for all stage pI NSCLC tumors with STAS compared with those without STAS ($p < 0.001$). (*B*) Overall survival is significantly reduced for all pathologic stage I NSCLC tumors with STAS compared with those without STAS ($p < 0.001$). NR, not reached; RFS, recurrence-free survival; OS, overall survival; STAS, spread through air spaces.

otherwise specified [NOS] [10.5%/19.3%], acinar or papillary [27.3%/29.8%], and micropapillary or solid [46.8%/19.3%] patterns) ($p < 0.0001$) (Table 4). The grade of the adenocarcinoma subtypes is summarized in Supplementary Table 3A. There were many contradictions between the grade provided from the contributing institutions and the traditional predominant grading system for nonmucinous adenocarcinomas of

Table 2. Univariate and Multivariable Analysis, Entire Cohort: Recurrence-Free Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	930/4061	23	2.47 (2.01-3.04)	<0.001
Age ≥65 (vs. <65) y	1911/4061	47	2.10 (1.73-2.56)	<0.001
Male (vs. female)	1801/4061	44	1.95 (1.60-2.37)	<0.001
Adenocarcinoma (vs. other histology)	3543/4061	87	0.40 (0.32-0.50)	<0.001
High grade (3/4 vs. 1/2)	870/3778	23	2.39 (1.95-2.92)	<0.001
Lymphovascular invasion (vs. none)	508/4032	13	3.70 (2.97-4.60)	<0.001
Size >3 cm (vs. ≤3 cm)	506/4061	12	2.30 (1.82-2.90)	<0.001
Visceral pleura invasion (vs. none)	746/4058	18	1.80 (1.46-2.22)	<0.001
Central T2 invasion (vs. none)	71/4061	2	2.32 (1.39-3.89)	<0.001
Sublobar resection (vs. lobectomy)	884/4061	22	1.14 (0.91-1.44)	0.257
Multivariable				
STAS present (vs. absent)	892/3760	24	1.62 (1.28-2.06)	<0.001
Age ≥65 (vs. <65) y	1779/3760	47	1.54 (1.25-1.90)	<0.001
Male (vs. female)	1650/3760	44	1.62 (1.32-1.99)	<0.001
Adenocarcinoma (vs. other NSCLC)	3356/3760	89	0.63 (0.48-0.83)	0.001
High grade (3/4 vs. 1/2)	864/3760	23	1.62 (1.31-2.01)	<0.001
Size >3 cm (vs. ≤3 cm)	460/3760	12	1.62 (1.34-2.21)	<0.001
Visceral pleura invasion (vs. none)	708/3760	19	1.28 (1.02-1.60)	0.036
Sublobar resection (vs. lobectomy) with LVI	105/3760	3	2.53 (1.66-3.88)	<0.001
Sublobar resection (vs. lobectomy) with no LVI	773/3760	21	1.05 (0.80-1.42)	0.748

Note: Cohort involves all patients undergoing R0 resection for stage pI NSCLC.
CI, 95% confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; n/N, number with the characteristic/total; STAS, spread through air spaces.

Table 3. Univariate and Multivariable Analysis, Entire Cohort: Overall Survival

Variable	n / N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	930/4061	23	2.74 (2.09-3.58)	<0.001
Age ≥65 (vs. <65) y	1911/4061	47	3.25 (2.47-4.28)	<0.001
Male (vs. female)	1801/4061	44	2.23 (1.72-2.90)	<0.001
Adenocarcinoma (vs. other histology)	3543/4061	87	0.30 (0.23-0.40)	<0.001
High grade (3/4 vs. 1/2)	870/3778	23	2.53 (1.95-3.30)	<0.001
Lymphovascular invasion (vs. none)	508/4032	13	4.12 (3.10-5.47)	<0.001
Size >3 cm (vs. ≤3 cm)	506/4061	12	2.22 (1.64-3.02)	<0.001
Visceral pleura invasion (vs. none)	746/4058	18	1.69 (1.28-2.24)	<0.001
Central T2 invasion (vs. none)	71/4061	2	1.21 (0.50-2.94)	0.672
Sublobar resection (vs. lobectomy)	884/4061	22	1.08 (0.79-1.48)	0.618
Multivariable				
STAS present (vs. absent)	892/3760	24	1.70 (1.24-2.33)	<0.001
Age ≥65 (vs. <65) y	1779/3760	47	2.36 (1.77-3.16)	<0.001
Male (vs. female)	1650/3760	44	1.66 (1.26-2.19)	<0.001
Adenocarcinoma (vs. other NSCLC)	3356/3760	89	0.51 (0.37-0.72)	<0.001
High grade (3/4 vs. 1/2)	864/3760	23	1.67 (1.26-2.21)	<0.001
Lymphovascular invasion (vs. none)	474/3760	13	2.21 (1.59-3.08)	<0.001
Size >3 cm (vs. ≤3 cm)	460/3760	12	1.44 (1.04-2.00)	0.029

Note: Cohort involves all patients undergoing R0 resection for stage pI NSCLC.
CI, 95% confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; n/N, number with the characteristic/total; STAS, spread through air spaces.

grade 1 = lepidic, grade 2 = acinar or papillary, and grade 3 = solid or micropapillary patterns. For example, almost half (43.6%) of the lepidic tumors were submitted as grades 2 to 4, rather than grade 1. It was difficult to imagine that a tumor that meets current WHO criteria for lepidic adenocarcinoma could be regarded as grade 3 or 4. However, stratifying by the submitted grade 1/2 versus 3/4 revealed the expected significant survival results. For this reason, we decided to stratify the survival analysis by the submitted data for grade rather than histologic subtype. Nevertheless, when we did multivariate analysis for each of the individual micropapillary-, solid-, acinar-, and papillary-predominant patterns of nonmucinous adenocarcinomas, we found that STAS remained independent in both RFS and OS (Supplementary Tables 4–7, respectively). The micropapillary pattern was significantly associated with RFS, but not OS by univariate analysis, but it was not significant by multivariable analysis for either RFS or OS (Supplementary Table 4). Nevertheless, the frequency of the micropapillary pattern was low at 1.9% of cases. The papillary pattern was not significant in univariate analysis for either RFS or OS (Supplementary Table 7). STAS was independent of lepidic-predominant

Table 4. Proportion With STAS by T Category and Adenocarcinoma Subtype

	Total		STAS			
Adenocarcinoma Subtype	N	% of all[a]	N Absent	N Present	% with STAS[b]	*p* Value
pT1 (n = 2619)						
Lepidic	632	24.1	583	49	7.8	<0.0001[c]
Acinar or papillary	1492	57.0	1084	408	27.3	
Micropapillary or solid	171	6.5	91	80	46.8	
Invasive mucinous or NOS	324	12.4	290	34	10.5	
pT2a (n = 924)						
Lepidic	97	10.5	90	7	7.2	<0.0001[c]
Acinar or papillary	624	67.5	438	186	29.8	
Micropapillary or solid	115	12.4	58	57	49.6	
Invasive mucinous or NOS	88	9.5	71	17	19.3	

Note: Distribution of histologic subtypes and proportion with STAS by T category and adenocarcinoma subtype. Cohort involves pT1 and pT2a N0M0R0 tumors.
[a]Column percent.
[b]Row percent.
[c]Chi-square *p* value (for difference in STAS presence by subtype with the T category).
Invasive mucinous, invasive mucinous adenocarcinoma; NOS, not otherwise specified; STAS, spread through air spaces.

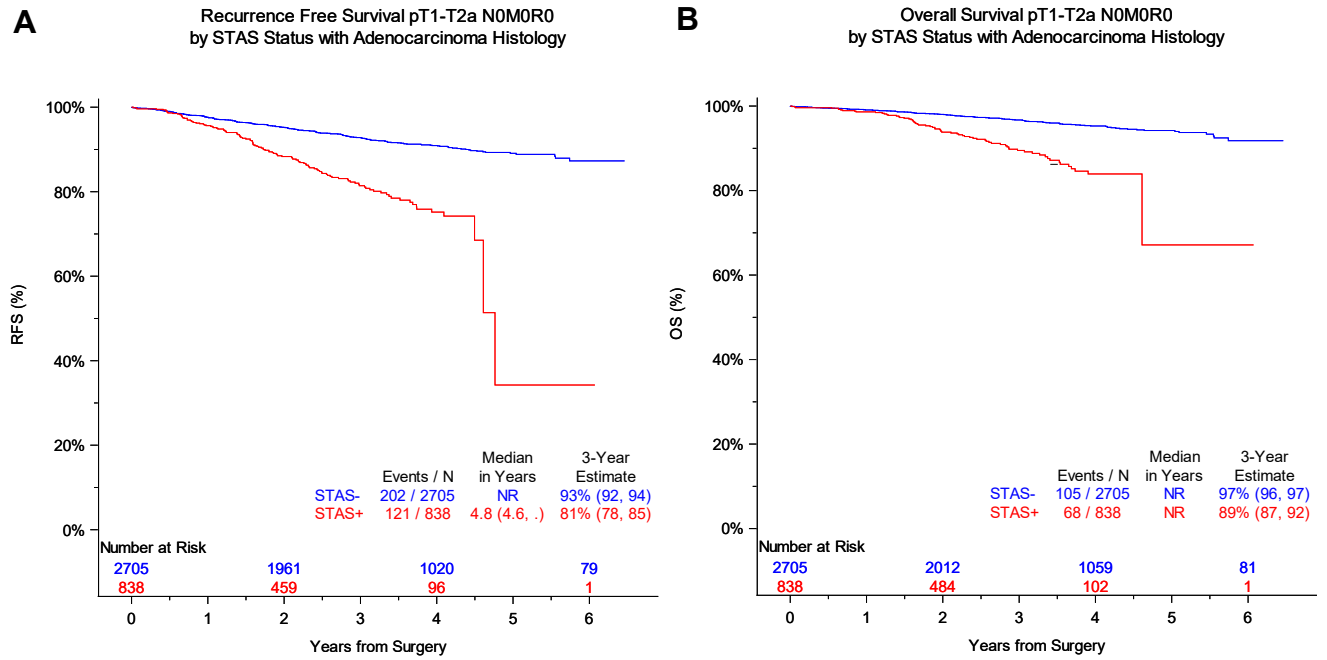

Figure 2. (*A*) Recurrence-free survival was significantly reduced for all stage pI adenocarcinoma patients when the tumors had STAS compared with those without STAS ($p < 0.001$). (*B*) Overall survival was significantly reduced for all patients with pathologic stage I adenocarcinoma when the tumors had STAS compared with those without STAS ($p < 0.0001$). NR, not reached; RFS, recurrence-free survival; OS, overall survival; STAS, spread through air spaces.

adenocarcinoma for RFS, but not for OS (Supplementary Table 8). These results of the multivariable analyses by histologic subtype are summarized in Supplementary Table 9.

Kaplan-Meier analysis revealed a 3-year RFS of 93% without STAS compared with 81% with STAS (Fig. 2*A*) ($p < 0.0001$) and a 3-year OS of 97% without STAS compared with 89% with STAS (Fig. 2*B*) ($p < 0.0001$).

In the regression analysis of patients with stage pI adenocarcinomas, STAS was significantly associated with poor prognosis by univariate ($p < 0.001/p < 0.001$) and multivariable ($p = 0.031/p = 0.032$) analysis for RFS

Table 5. Univariate and Multivariable Analysis, Adenocarcinoma: Recurrence-Free Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	838/3543	24	2.79 (2.22-3.51)	<0.001
Age ≥65 (vs. <65) y	1592/3543	45	2.11 (1.69-2.63)	<0.001
Male (vs. female)	1415/3543	40	1.82 (1.46-2.27)	<0.001
High grade (3/4 vs. 1/2)	684/3371	20	2.72 (2.17-3.41)	<0.001
Lymphovascular invasion (vs. none)	402/3519	11	4.37 (3.41-5.60)	<0.001
Size >3 cm (vs. ≤3 cm)	373/3543	11	2.45 (1.86-3.23)	<0.001
Visceral pleura invasion (vs. none)	665/3540	19	2.07 (1.64-2.61)	<0.001
Central T2 invasion (vs. none)	36/3543	1	1.98 (0.88-4.44)	0.091
Sublobar resection (vs. lobectomy)	796/3543	22	1.17 (0.90-1.52)	0.233
Multivariable				
STAS present (vs. absent)	826/3356	25	1.49 (1.15-1.94)	0.031
Age ≥65 (vs. <65) y	1537/3356	46	1.54 (1.22-1.95)	0.003
Male (vs. female)	1352/3356	40	1.64 (1.31-2.05)	<0.001
High grade (3/4 vs. 1/2)	680/3356	20	2.05 (1.62-2.59)	<0.001
Lymphovascular invasion (vs. none)	399/3356	12	2.44 (1.83-3.25)	<0.001
Size >3 cm (vs. ≤3 cm)	357/3356	11	1.87 (1.41-2.50)	<0.001
Sublobar resection (vs. lobectomy) with VPI	101/3356	3	2.38 (1.49-3.78)	<0.001
Sublobar resection (vs. lobectomy) with no VPI	693/3356	21	1.16 (0.84-1.60)	0.357

Note: Cohort involves adenocarcinoma, stage pI, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces; VPI, visceral pleural invasion.

Table 6. Univariate and Multivariable Analysis, Adenocarcinoma: Overall Survival

Variable	n / N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	838/3543	24	3.24 (2.37-4.44)	<0.001
Age ≥65 (vs. <65) y	1592/3543	45	3.39 (2.46-4.67)	<0.001
Male (vs. female)	1415/3543	40	2.15 (1.59-2.90)	<0.001
High grade (3/4 vs. 1/2)	684/3371	20	2.98 (2.20-4.04)	<0.001
Lymphovascular invasion (vs. none)	402/3519	11	5.31 (3.82-7.40)	<0.001
Size >3 cm (vs. ≤3 cm)	373/3543	11	2.32 (1.59-3.39)	<0.001
Visceral pleura invasion (vs. none)	665/3540	19	1.96 (1.43-2.70)	<0.001
Central T2 invasion (vs. none)	36/3543	1	1.68 (0.54-5.27)	0.369
Sublobar resection (vs. lobectomy)	796/3543	22	1.04 (0.72-1.50)	0.833
Multivariable				
STAS present (vs. absent)	826/3356	25	1.49 (1.03-2.13)	0.032
Age ≥65 (vs. <65) y	1537/3356	46	2.55 (1.82-3.57)	<0.001
Male (vs. female)	1352/3356	40	1.88 (1.38-2.55)	<0.001
High grade (3/4 vs. 1/2)	680/3356	20	2.22 (1.62-3.04)	<0.001
Lymphovascular invasion (vs. none)	399/3356	12	2.89 (1.99-4.20)	<0.001

Note: Cohort involves adenocarcinoma, stage pI, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces; VPI, visceral pleural invasion.

and OS, respectively (Tables 5 and 6). Of note, in multivariable analysis, STAS remained an independent prognostic factor after adjusting for multiple factors including age, sex, grade, and LVI. LVI remained an independent factor in RFS and OS. An interaction between extent of resection and VPI was detected in RFS but not OS, where extent of resection was significantly associated with RFS among patients with VPI, but not among patients without VPI (Tables 5 and 6). Regardless, STAS remained statistically associated with RFS after accounting for this interaction.

Other Non–Small Cell Carcinomas. Among patients with stage pI "other NSCLC" histologic types, Kaplan-Meier analysis revealed that STAS was associated with a significantly reduced 3-year RFS of 67% compared with 79% without STAS ($p = 0.008$) (Fig. 3*A*) and a significantly reduced OS of 71% compared with 86%

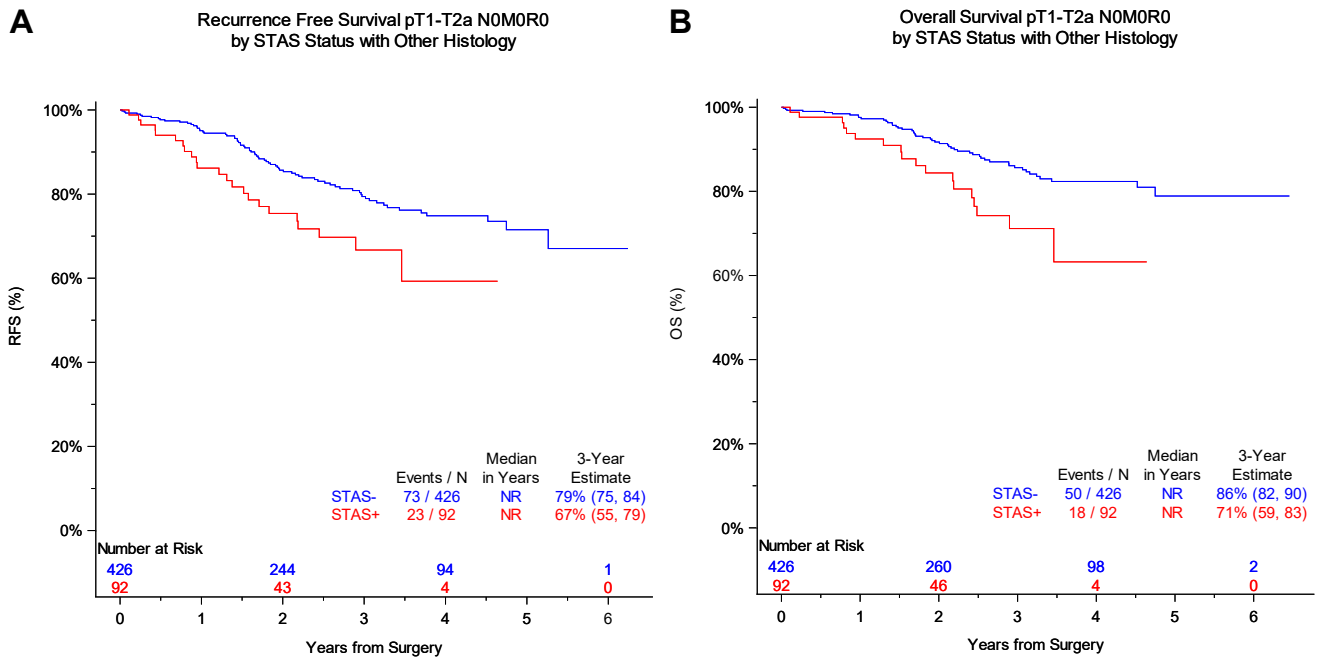

Figure 3. (*A*) Recurrence-free survival was significantly reduced for all patients with stage pI NSCLC with other NSCLC when the tumors had STAS compared with those without STAS ($p = 0.008$). (*B*) Overall survival was significantly reduced for all patients with pathologic stage I NSCLC with other NSCLC when the tumors had STAS compared with those without STAS ($p = 0.004$). NR, not reached; RFS, recurrence-free survival; OS, overall survival; STAS, spread through air spaces.

Table 7. Univariate and Multivariable Analysis, Other NSCLC: Recurrence-Free Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	92/518	18	1.89 (1.17-3.03)	0.008
Age ≥65 (vs. <65) y	319/518	62	1.43 (0.93-2.18)	0.101
Male (vs. female)	386/518	75	1.17 (0.72-1.90)	0.525
High grade (3/4 vs. 1/2)	186/407	46	0.81 (0.52-1.25)	0.340
Lymphovascular invasion (vs. none)	106/513	21	1.57 (0.98-2.49)	0.056
Size >3 cm (vs. ≤3 cm)	133/518	26	1.23 (0.79-1.91)	0.362
Visceral pleura invasion (vs. none)	81/518	16	1.14 (0.67-1.92)	0.634
Central T2 invasion (vs. none)	35/518	7	1.40 (0.70-2.80)	0.343
Sublobar resection (vs. lobectomy)	88/518	17	1.44 (0.85-2.43)	0.172
Multivariable				
STAS present (vs. absent)	66/404	16	1.91 (1.13-3.25)	0.015

Note: Cohort involves other NSCLC, stage pI, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

without STAS ($p = 0.004$) (Fig. 3*B*). The grade of the "other NSCLC" histologic types is summarized in Supplementary Table 3B.

STAS was associated with poor prognosis by univariate ($p = 0.008/p = 0.004$) and multivariable ($p = 0.015/p = 0.017$) analysis for RFS and OS, respectively (Tables 7 and 8). It was independent of age, sex, grade, extent of resection, and LVI. Only STAS, but not LVI or VPI, was an independent predictor of poor prognosis.

Extent of Surgical Resection

Lobar Resection. In the 3177 stage pI tumors where the surgical procedure was lobectomy, 693 (21.8%) had STAS (Table 1). Patients undergoing lobectomy had a 3-year RFS of 91% without STAS compared with 82% with STAS (Fig. 4*A*) ($p < 0.001$) and a 3-year OS of 95% without STAS compared with 89% with STAS (Fig. 4*B*) ($p < 0.001$).

On correcting for potential confounding factors, STAS remained significantly associated with worse prognosis in both univariate ($p < 0.001/p < 0.001$) and multivariable ($p = 0.011/p = 0.011$) analyses for both RFS and OS, respectively (Tables 9 and 10). For RFS and OS, STAS was independent of age, sex, histology (adenocarcinoma versus other NSCLC), grade, size, and LVI. LVI but not VPI was an independent predictor of poor survival in multivariable analysis for both RFS and OS.

Sublobar Resection. In the 884 pathologic stage I NSCLC where the surgical procedure was segmentectomy or wedge resection, 237 (26.8 %) had STAS (Table 1). Patients undergoing sublobar resection had a 3-year RFS of 92% without STAS compared with 73% with STAS (Fig. 5*A*) ($p < 0.0001$) and a 3-year OS of 96% without STAS compared with 83% with STAS (Fig. 5*B*) ($p < 0.0001$).

STAS remained significantly associated with worse prognosis in both univariate ($p < 0.001/p < 0.001$) and multivariable ($p = 0.001/p = 0.009$) analysis for both RFS/OS, respectively (Tables 11 and 12). For RFS and OS, STAS was independent of age, sex, histology (adenocarcinoma versus other NSCLC), grade, and LVI. Although LVI was retained as an independent predictor of poor RFS and OS, VPI was not.

Table 8. Univariate and Multivariable Analysis, Other NSCLC: Overall Survival

Variable	n / N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	92/518	18	2.17 (1.26-3.75)	0.004
Age ≥65 (vs. <65) y	319/518	62	1.87 (1.10-3.17)	0.019
Male (vs. female)	386/518	75	0.95 (0.55-1.65)	0.869
High grade (3/4 vs. 1/2)	186/407	46	0.74 (0.43-1.27)	0.276
Lymphovascular invasion (vs. none)	106/513	21	1.44 (0.82-2.52)	0.207
Size >3 cm (vs. ≤3 cm)	133/518	26	1.12 (0.66-1.90)	0.684
Visceral pleura invasion (vs. none)	81/518	16	1.26 (0.69-2.32)	0.448
Central T2 invasion (vs. none)	35/518	7	0.39 (0.10-1.59)	0.174
Sublobar resection (vs. lobectomy)	88/518	17	1.76 (0.98-3.18)	0.056
Multivariable				
STAS present (vs. absent)	66/404	16	2.12 (1.13-3.98)	0.017

Note: Cohort involves other NSCLC, stage pI, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

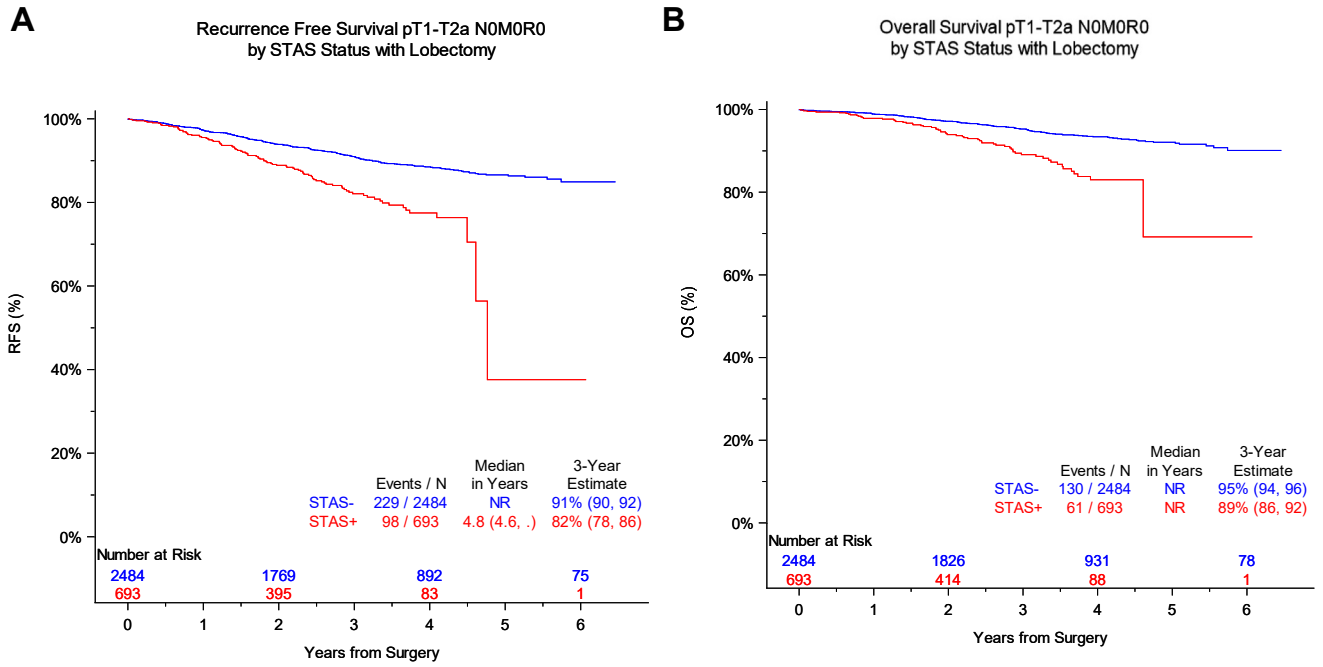

Figure 4. (*A*) Recurrence-free survival was significantly reduced for all patients with stage pI NSCLC who underwent lobectomy or bilobectomy when the tumors had STAS compared with those without STAS ($p < 0.001$). (*B*) Overall survival was significantly reduced for all patients with pathologic stage I NSCLC who underwent lobectomy or bilobectomy when the tumors had STAS compared with those without STAS ($p < 0.001$). NR, not reached; RFS, recurrence-free survival; OS, overall survival; STAS, spread through air spaces.

When included in multivariable analysis for the sublobar resection group, there was no difference in outcome between segmentectomy versus wedge resection either by RFS or OS (Supplementary Table 10).

Overview of Multivariable Analyses. To provide an overview of the results, tables were generated for RFS and OS to summarize the hazard ratios from the multivariable analyses (Supplementary Table 11).

Discussion

On the basis of the IASLC database, for the ninth edition of the TNM classification of lung cancer,[29] we have revealed that STAS is an independent predictor of

Table 9. Univariate and Multivariable Analysis, Lobectomy Cohort: Recurrence-Free Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	693/3177	22	2.08 (1.64-2.65)	<0.001
Age ≥65 (vs. <65) y	1432/3177	45	1.96 (1.58-2.45)	<0.001
Male (vs. female)	1431/3177	45	1.91 (1.53-2.38)	<0.001
Adenocarcinoma (vs. other NSCLC)	2747/3177	86	0.41 (0.32-0.53)	<0.001
High grade (3/4 vs. 1/2)	699/2948	24	2.35 (1.87-2.94)	<0.001
Lymphovascular invasion (vs. none)	403/3154	13	3.00 (2.32-3.88)	<0.001
Size >3 cm (vs. ≤3 cm)	479/3177	15	2.43 (1.90-3.10)	<0.001
Visceral pleura invasion (vs. none)	630/3176	20	1.66 (1.31-2.10)	<0.001
Central T2 invasion (vs. none)	67/3177	2	2.34 (1.37-4.00)	0.001
Multivariable				
STAS present (vs. absent)	665/2936	23	1.43 (1.08-1.88)	0.011
Age ≥65 (vs. <65) y	1331/2936	45	1.52 (1.20-1.91)	<0.001
Male (vs. female)	1314/2936	45	1.51 (1.20-1.91)	<0.001
Adenocarcinoma (vs. other NSCLC)	2598/2936	88	0.65 (0.48-0.87)	0.004
High grade (3/4 vs. 1/2)	695/2936	24	1.75 (1.38-2.22)	<0.001
Lymphovascular invasion (vs. none)	376/2936	13	1.93 (1.44-2.59)	<0.001
Size >3 cm (vs. ≤3 cm)	436/2936	15	1.85 (1.43-2.41)	<0.001

Note: Cohort involves patients undergoing lobectomy for stage pI NSCLC, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

Table 10. Univariate and Multivariable Analysis, Lobectomy Cohort: Overall Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	693/3177	22	2.42 (1.77-3.30)	<0.001
Age ≥65 (vs. <65) y	1432/3177	45	3.04 (2.25-4.12)	<0.001
Male (vs. female)	1431/3177	45	2.25 (1.68-3.02)	<0.001
Adenocarcinoma (vs. other NSCLC)	2747/3177	86	0.32 (0.24-0.44)	<0.001
High grade (3/4 vs. 1/2)	699/2948	24	2.38 (1.77-3.19)	<0.001
Lymphovascular invasion (vs. none)	403/3154	13	3.27 (2.35-4.56)	<0.001
Size >3 cm (vs. ≤3 cm)	479/3177	15	2.29 (1.66-3.17)	<0.001
Visceral pleura invasion (vs. none)	630/3176	20	1.55 (1.13-2.12)	0.006
Central T2 invasion (vs. none)	67/3177	2	1.02 (0.38-2.74)	0.973
Multivariable				
STAS present (vs. absent)	665/2936	23	1.59 (1.11-2.28)	0.011
Age ≥65 (vs. <65) y	1331/2936	45	2.29 (1.67-3.15)	<0.001
Male (vs. female)	1314/2936	45	1.68 (1.23-2.30)	<0.001
Adenocarcinoma (vs. other NSCLC)	2598/2936	88	0.53 (0.37-0.77)	<0.001
High grade (3/4 vs. 1/2)	695/2936	24	1.64 (1.20-2.23)	0.002
Lymphovascular invasion (vs. none)	376/2936	13	1.86 (1.28-2.72)	0.001
Size >3 cm (vs. ≤3 cm)	436/2936	15	1.57 (1.11-2.22)	0.010

Note: Cohort involves patients undergoing lobectomy for stage pI NSCLC, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

poor prognosis in R0 surgically resected stage pI NSCLC. This was true in multivariable analysis for both RFS and OS in all patients with NSCLC regardless of extent of resection (lobectomy or sublobar resection) or histologic type (adenocarcinoma or other NSCLC). Our finding that STAS has prognostic value is supported by other many studies as summarized in several meta-analyses.[4–8] In our multivariable analysis, we sought to explore whether STAS was an independent prognostic factor when compared with other histologic descriptors currently recognized by the TNM classification including VPI or LVI.[21–23,30] Based on our results, we recommend that STAS be added as a new T histologic descriptor for the forthcoming Ninth Edition TNM Classification[24];

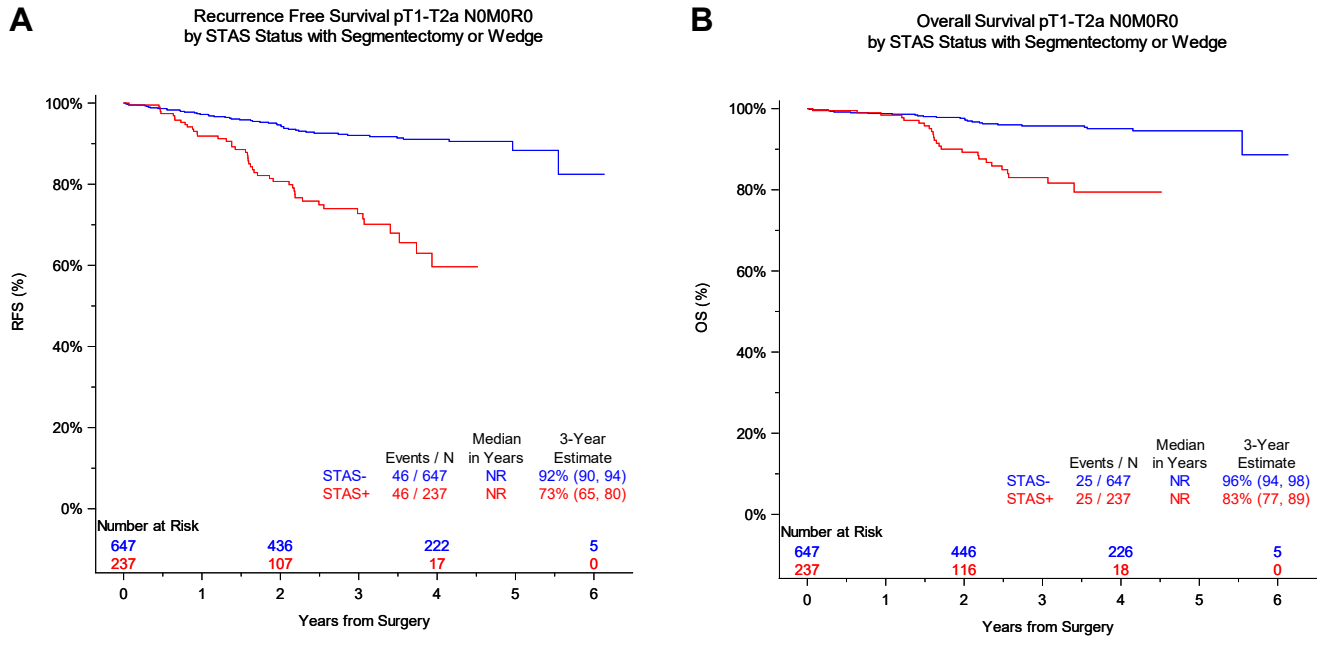

Figure 5. (*A*) Recurrence-free survival was significantly reduced for all patients with stage pI NSCLC who underwent sublobar resection when the tumors had STAS compared with those without STAS ($p < 0.001$). (*B*) Overall survival was significantly reduced for all patients with pathologic stage I NSCLC who underwent wedge resection or segmentectomy when the tumors had STAS compared with those without STAS ($p < 0.001$). NR, not reached; RFS, recurrence-free survival; OS, overall survival; STAS, spread through air spaces.

Table 11. Univariate and Multivariable Analysis, Sublobar Cohort: Recurrence-Free Survival

Variable	n/N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	237/884	27	4.19 (2.76-6.37)	<0.001
Age ≥65 (vs. <65) y	479/884	54	2.73 (1.73-4.30)	<0.001
Male (vs. female)	370/884	42	2.15 (1.42-3.25)	<0.001
Adenocarcinoma (vs. other NSCLC)	796/884	90	0.34 (0.20-0.57)	<0.001
High grade (3/4 vs. 1/2)	171/830	21	2.61 (1.68-4.04)	<0.001
Lymphovascular invasion (vs. none)	105/878	12	7.96 (5.13-12.35)	<0.001
Size >3 cm (vs. ≤3 cm)	27/884	3	2.52 (1.02-6.21)	0.038
Visceral pleura invasion (vs. none)	116/882	13	2.70 (1.71-4.25)	<0.001
Central T2 invasion (vs. none)	4/884	0	3.05 (0.42-22.00)	0.243
Multivariable				
STAS present (vs. absent)	227/824	28	2.22 (1.36-3.60)	0.001
Age ≥65 (vs. <65) y	448/824	54	1.76 (1.09-2.84)	0.020
Male (vs. female)	336/824	41	1.91 (1.24-2.93)	0.003
Lymphovascular invasion (vs. none)	98/824	12	5.02 (3.03-8.34)	<0.001

Note: Cohort involves patients undergoing sublobar resection of stage pI NSCLC, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

however, we do not regard these data to be sufficient to include STAS into stage grouping. Although this has been proposed by others,[10,12,18] STAS will not be incorporated into proposals for stage groupings in the forthcoming edition of the TNM Classification for lung cancer.[31]

Although STAS was found to be consistently associated with OS and RFS in all subgroups evaluated, we were surprised to find that the association between VPI and survival outcomes was less consistent in multivariable models. VPI was either an independent predictor or effect modifier in only two of the 10 RFS subgroup analyses (all NSCLC and adenocarcinoma) and was not found to be associated with OS in any subgroup after adjustment. VPI is an established factor that has been used to upstage T1 tumors to T2 category for the past 46 years since the first AJCC TNM classification of lung cancers in 1977.[23,24,32–38] Although, STAS was first described in 2015, we were able to assess the impact of STAS in comparison with other histologic descriptors such as LVI and VPI. These analyses suggest that STAS and LVI may be stronger predictors of outcome than VPI.

Similar to our findings, in studies that included both STAS and VPI in multivariable analysis, STAS seemed to outperform VPI as a predictor for poor outcome. In most studies where both factors were analyzed, STAS, but not VPI, was retained as an independent factor.[9,11,39–48] In a few studies, both STAS and VPI were independent variables for survival.[42,43] In two of these studies, the results varied between RFS and OS.[42,43] One potential explanation for why STAS might outperform VPI in predicting survival is that VPI can only be found in tumors in contact with the visceral pleura, whereas STAS can be

Table 12. Univariate and Multivariable Analysis, Sublobar Cohort: Overall Survival

Variable	n / N	%	HR (95% CI)	*p* Value
Univariate				
STAS present (vs. absent)	237/884	27	4.09 (2.32-7.20)	<0.001
Age ≥65 (vs. <65) y	479/884	54	4.59 (2.27-9.26)	<0.001
Male (vs. female)	370/884	42	2.24 (1.27-3.94)	0.004
Adenocarcinoma (vs. other NSCLC)	796/884	90	0.19 (0.10-0.36)	<0.001
High grade (3/4 vs. 1/2)	171/830	21	3.29 (1.82-5.96)	<0.001
Lymphovascular invasion (vs. none)	105/878	12	9.41 (5.28-16.77)	<0.001
Size >3 cm (vs. ≤3 cm)	27/884	3	2.89 (0.90-9.31)	0.062
Visceral pleura invasion (vs. none)	116/882	13	2.58 (1.39-4.79)	0.002
Central T2 invasion (vs. none)	4/884	0	6.46 (0.89-47.18)	0.034
Multivariable				
STAS present (vs. absent)	227/824	28	2.43 (1.23-4.81)	0.009
Age ≥65 (vs. <65) y	448/824	54	2.87 (1.33-6.19)	0.005
Adenocarcinoma (vs. other NSCLC)	758/824	92	0.37 (0.17-0.82)	0.012
Lymphovascular invasion (vs. none)	98/824	12	4.53 (2.28-8.98)	<0.001

Note: Cohort involves patients undergoing sublobar resection of stage pI NSCLC, R0.
CI, 95% confidence interval; HR, hazard ratio; n/N, number with the characteristic/total; STAS, spread through air spaces.

observed not only in tumors with VPI but also those deep within the alveolar parenchyma. Further studies are needed to confirm the relative importance of STAS and LVI in relation to VPI.

Although the difference was not statistically significant, the finding that STAS was found less often in central T2 tumors is logical because tumors in this location are more likely to be endobronchial. Tumors partially or completely surrounded by a bronchus have less interface with the adjacent alveolar parenchyma, and thus they are less likely to have STAS.

Recommendation to Add STAS as a Histologic T Descriptor for Lung Cancer

Staging of cancer is the practice of classifying cancer according to the anatomic extent of tumor.[49] As the presence of STAS reflects the anatomic extension of tumor into the surrounding lung parenchyma, it is appropriate to consider that it might be useful in lung cancer staging. The UICC and AJCC already recognize LVI and Pn as additional descriptors in the TNM Classifications.[22,23,25,30] VPI is an established descriptor that is typically recognized histologically, resulting in T1 tumors to be upstaged to T2a.[23,30,49] Now, based on these new data in the IASLC Lung Cancer Staging Project collected in preparation for the ninth edition of the TNM classification for lung cancer, we reveal results that support adding STAS as a histologic descriptor along with the currently recognized VPI, LVI, and Pn.[23,30,50] It is already recommended to collect data on STAS in the lung cancer synoptic templates proposed by the College of American Pathologists and the International Collaboration on Cancer Reporting.[51,52] On the basis of the recommendations of these leading organizations, and the results of our data, the presence or absence of STAS should be documented systematically in pathology reports of resected lung cancers. Hopefully, it will become a standard element in lung cancer synoptic reports around the world.

Just as VPI is a T descriptor specific only to lung cancer,[23,30] our recommendation is that STAS be added as a histologic descriptor only for lung cancer. This is because of the unique properties of the lung, in which, unlike any other organ system, alveolar spaces can surround the tumor thus providing a compartment of the lung into which tumor cells may spread. For clinical staging, it is not possible to consider adding STAS as a clinical descriptor, because it is a microscopic finding that cannot be found on computed tomography (CT) imaging. Multiple studies have used standard imaging characteristics or radiomics attempting to preoperatively predict the probability of existence of STAS,[53–56] Nevertheless, these studies have mainly used surrogate markers that correspond to aggressiveness of lung cancers such as pulmonary vessel convergence, spiculation, solid component, pleural indentation, mediastinal adenopathy, or pleural thickening.[57] The resolution of CT scans is not high enough to detect the small nests of tumor cells of STAS. In the absence of a way to definitively identify STAS by imaging, it cannot be recognized in clinical staging of lung cancer.

Our study did not analyze the IASLC Lung Cancer Staging Project for STAS in neuroendocrine lung tumors including typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma. There is a separate subcommittee of the SPFC who will be analyzing the neuroendocrine tumors in the IASLC database. Nevertheless, previous work has revealed that STAS is an independent predictor of prognosis for large cell neuroendocrine carcinoma and small cell carcinoma.[14,58]

T Descriptors

We have previously recommended that STAS should not be incorporated into measurement of tumor size for several reasons.[50,59] This would require microscopic measurement from the furthest STAS tumor cells on one side of the tumor to the furthest STAS on the opposite side of the tumor at its maximum dimension. It may be challenging to measure the distance of STAS tumor cells that are the furthest from the tumor edge, due to the frequent collapse of peritumoral alveolar parenchyma. In some cases, the STAS cells may extend beyond the amount of nonneoplastic lung parenchyma surrounding the tumor on a given slide. When this occurs, it may be very difficult or impossible to measure the distance of furthest STAS from the tumor edge when these tumor clusters are on different histologic section. Because STAS cannot be appreciated by CT, it also could lead to greater discrepancy between clinical tumor size assessed by CT imaging and pathologic measurement of tumor size. Thus, tumor size should continue to be measured according to the gross or microscopically recognized edge of lung cancers, with adjustment for invasive size in part-lepidic nonmucinous adenocarcinomas, rather than according to the maximum distance of furthest STAS.

STAS and Extent of Surgical Resection

We found that STAS was an independent predictor of outcome when analyzed within the lobectomy and sublobar resection cohorts. A similar result was found in the meta-analysis by Liu et al.[6] where it was found that the presence of STAS correlated with lower RFS both in patients who underwent lobectomies and sublobar resections, with a higher hazard ratio for recurrence in sublobar resections (3.648 versus 1.865).

We also observed interactions with lobectomy versus sublobar resection in RFS rather than OS, with LVI in all NSCLC and with VPI in adenocarcinomas. This study was not designed to address the implications of STAS for determining optimal surgical management for patients with lung cancer. Issues regarding surgical management are an important topic for future study.

Histologic Grade and STAS

Our results also indicated that the prognostic significance of STAS was independent of histologic grade for all NSCLC and in the analyses specifically evaluating adenocarcinoma and other NSCLC. Histologic grade, as provided by the contributing institutions, remained an independent predictor of outcome, in the analyses of the (1) overall NSCLC, (2) adenocarcinoma, and (3) lobectomy subgroups. Nevertheless, grade was not significant by multivariable analysis for the other NSCLC and sublobar resection subgroups. In adenocarcinomas, grade had a higher hazard ratio compared with STAS, although STAS remained an independent factor for both RFS and OS. Because the data for grade matched the expected patient outcome and the submitted data for grade did not correspond to current concepts of predominant adenocarcinoma histologic subtyping with almost half of lepidic adenocarcinomas being graded as 2, 3, or 4, it was decided to use grade rather than predominant histologic subtype for survival analyses. The low frequency of the micropapillary-predominant pattern, found in less than 2% of adenocarcinomas, is lower than the 6% found in a meta-analysis by Pyo et al.[60] and in other studies.[61–63] This raises the question whether the submitted micropapillary pattern data may have been underreported, and this may have affected the survival analysis. We found that STAS was an independent prognostic marker by RFS and OS for the micropapillary-, solid-, acinar-, and papillary-predominant patterns of nonmucinous adenocarcinomas. The proposed IASLC grading system for nonmucinous lung adenocarcinomas could not be implemented because it was published in 2020 and adopted by the 2021 WHO Classification both of which were published after the data collection was closed in 2019.[2,27] Furthermore, the IASLC SPFC database did not collect the percentages of all histologic subtypes, so we could not retrospectively reconstruct that grading system.

High-grade histologic subtypes of lung adenocarcinoma such as micropapillary and solid patterns are also known to be associated with lymphatic and vascular invasion.[64–66] So, it is no surprise that this association would also be found with another predictor of poor prognosis such as STAS. Recent data from the TRACERx lung adenocarcinoma cohort revealed that disease-free survival was shorter not only for STAS-positive tumors compared with STAS-negative tumors, but it also was associated with an increased risk only of intrathoracic but not extrathoracic recurrence.[67] Further study is needed to address the relative importance of STAS, LVI, and VPI in determining intrathoracic versus extrathoracic recurrence.

Criteria for STAS

Data on the criteria for STAS used by the various institutions contributing data to the IASLC Lung Cancer Staging Project were not available; however, it is likely that most used the original criteria defined by Kadota et al.[1] and the 2015 and 2021 WHO classification,[2,3] because these seem to be the most frequently used in the published articles. The original definition of STAS by Kadota et al. and the 2015 WHO classification consisted of tumor cells within the first alveolar spaces in the lung parenchyma beyond the edge of the main tumor.[1] In adenocarcinoma, it can occur as one of three morphologic patterns, including (1) micropapillary structures within air spaces, (2) solid nests or tumor islands, and (3) scattered discohesive single cells.[1–3] An important component of the diagnostic criteria that were included in the original description of STAS is the distinction from artifacts.[1] The following features favor an artifact: (1) mechanically induced tumor floaters that are randomly situated often at the edge of the tissue section or out of the plane of section; (2) jagged edges of tumor cell clusters suggesting fragmentation or edges of a knife cut during specimen processing; (3) isolated tumor clusters at a distance from the tumor rather than spreading in a continuous manner from the tumor edge; and (4) linear strips of cells lifted off alveolar walls.[1–3] Although it is recognized that in some cases it may be challenging to separate STAS from artifacts, regardless of any debate about its mechanism, the consistent finding that STAS is an independent prognostic factor in all of our analyses supports that it is a clinically useful histologic factor.[68] Recognition of STAS requires a sample of tumor with the border of the tumor, and STAS tumor cells in the surrounding lung parenchyma, so small biopsy, or cytology specimens should not be obtained to identify STAS.

Similar to the TNM recommendations for assessment of other histologic descriptors such as LVI, and Pn, by the AJCC and UICC,[25,69] STAS was recorded as present or absent without any grading of extent. Published data regarding the prognostic significance of STAS focusing on the extent, rather than just positive versus negative, have used various proposed grading schemes and quantification methods. These have not consistently revealed prognostic significance with some revealing

correlations with differences in outcome and others failing to do so.[11,39,42,70–74] For TNM purposes, we recommend to follow the format of UICC and AJCC recommendations for the other histologic descriptors, so STAS should be recorded as present, absent, or unknown.[25,26]

Data Representing Worldwide Clinical Practice

The IASLC SPFC database with over 4000 patients evaluable for STAS is the largest cohort to be analyzed to this point in time, representing data from a set of pathologic stage I R0 NSCLC that reflects the routine clinical practice of pathologists from around the world. In particular, the data were based on the IASLC SPFC database, so the results represented the real-world data submitted in recent years, suggesting the clinical feasibility and usefulness of histologic assessment of STAS. This differs from most of the currently published studies where investigators from individual institutions collected data on STAS to analyze lung cancer resections for the prognostic significance of STAS.[9,10,12,39,41,42,75,76]

A lower frequency of STAS was observed in the data from Asia and the rest of the world (ROW) compared with North America and Europe. This likely represents underreporting of STAS rather than a lower incidence as many of the papers published about the prognostic significance of STAS are from Japan and China, and they have more comparable frequencies to that found in the North American and European cohorts in the IASLC Ninth Edition database.[12,39,41,77–80] Because lung cancers submitted to the IASLC database were diagnosed beginning in 2011, 4 to 5 years before STAS was even described, this lower frequency could be due to a variety of causes including slow implementation of pathologists recording STAS in their pathology reports and/or lack of updating of the pathology fields collected in the databases provided to the IASLC Lung Cancer Staging Project. Because we found that STAS is significant in all our analyses, despite this low frequency in Asia and ROW, it is possible that the results might even be stronger if we had reporting of STAS at the higher frequency documented in the publications from Japan and China.

Summary

In summary, analysis of the IASLC ninth edition database confirms the prognostic significance of STAS in a worldwide cohort of 4061 patients with pathologic stage I R0 NSCLC. These results and the extensive published data[4–7,53,81] support our proposal to add STAS as a histologic descriptor for the ninth edition of the TNM classification of lung cancer. Hopefully, this will elevate the recognition of STAS around the world, so carefully annotated data can be collected by the IASLC Lung Cancer Staging Project to enable evaluation of the relative importance of STAS versus VPI in lung cancer staging for development of the tenth edition of the TNM classification. To achieve this important objective, the IASLC SPFC counts on the continuous international collaboration of as many institutions as possible and wholeheartedly acknowledges their voluntary contribution of data to the IASLC Lung Cancer Staging Project.

Several important issues not addressed by this manuscript are whether STAS could affect stage groupings similar to VPI, whether the identification of STAS might influence extent of surgery, and how STAS might be incorporated into the R classification. Further studies are needed to address these questions.

CRediT Authorship Contribution Statement

William D. Travis: Data curation, Investigation, Formal analysis, Writing—original draft.

Megan Eisele: Data curation, Investigation, Formal analysis, Writing—review and editing.

Katherine K. Nishimura: Data curation, Investigation, Formal analysis, Writing—review and editing.

Rania Aly: Data curation, Writing—review and editing.

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Philippe Joubert: Writing—review and editing.

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Paula Ugalde: Writing—review and editing.

Paul Van Schil: Writing—review and editing.

Jeff Yang: Writing—review and editing.

Vanessa J. Cilento: Data curation, Investigation, Formal analysis.

Masaya Yotsukura: Writing—review and editing.

Hisao Asamura: Data curation, Investigation, Writing—review and editing.

Disclosure

Dr. Donington reports receiving personal fees from Amgen, AstraZeneca, Bristol Myers Squibb, Merck & Co., Inc., and Genentech, Inc./F. Hoffmann-La Roche Ltd., outside the submitted work. Dr. Joubert reports grants from AstraZeneca, Roche, Merck and Biomark Signature Inc. and personal fees from AstraZeneca and Merck, outside the submitted work. Dr. Mino-Kenudson reports receiving personal fees from AstraZeneca, Pfizer, Repare, Sanofi, AbbVie, Daiichi Sankyo, Boehringer Ingelheim, and Elsevier, outside the submitted work. Dr. Nishimura reports receiving grants from IASLC, outside the submitted work. Dr. Nicholson reports receiving personal fees from Merck, Boehringer Ingelheim, Novartis, AstraZeneca, Bristol Myers Squibb, Roche, AbbVie, Oncologica, UpToDate, the European Society of Oncology, Liberum, Takeda UK, and Sanofi and grants and personal fees from Pfizer, outside the submitted work. Dr. Papotti reports receiving personal fees from Roche, Eli Lilly, AstraZeneca, and Pfizer, outside the submitted work. Dr. Ugalde Figueroa reports receiving personal fees from AstraZeneca, Bristol, Roche, Medtronic, and Johnson & Johnson, outside the submitted work. Dr. Van Schil reports receiving personal fees from AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme, Roche, and Janssen, outside the submitted work; and serving as President of International Association for the Study of Lung Cancer and Treasurer of Belgian Association for Cardiothoracic Surgery. Dr. Yang reports being on advisory boards for AstraZeneca and Genentech. He has also received honorarium from AstraZeneca, outside the submitted work. Dr. Lievens reports financing from the EU ImmunoSABR project, personal fees from the UpLung project, AstraZeneca, outside the submitted work.

Acknowledgments

The authors acknowledge Patricia Vigues for her great help in coordinating the entire TNM SPFC project for IASLC. The authors also gratefully acknowledge all the many contributing investigators and institutions who provided the data for this analysis.

Funding

Drs. Travis, Aly, and Rusch were supported by the Memorial Sloan Kettering Cancer Center National Cancer Institute Support Core Grant: P30 CA008748.

Appendix 1.

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Appendix 2. Chairpersons and Members of the Subcommittees of the Lung Cancer, Thymic Epithelial Tumors, Pleural Mesothelioma, and Esophageal Cancer Domains of the IASLC Staging and Prognostic Factors Committee

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Lung Cancer Domain Neuroendocrine Tumors Subcommittee. Ming Tsao (chair), Andrew G. Nicholson, (co-chair), Ricardo Beyruti, Frank Detterbeck, Wilfried

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Lung Cancer Domain Prognostic Factors Subcommittee. Frank Detterbeck (chair), Raymond U. Osarogiagbon (co-chair), Alex Brunelli, Kwun Fong, Meredith Giuliani, James Huang, Young Tae Kim, Mark Krasnik, Hiu Liu, Jan van Meerbeeck, Luis M. Montuenga, Andrew G. Nicholson, Paul Martin Putora, Valerie Rusch, Robert Samstein, Navneet Singh, Martin Tammemägi, Ricardo Terra, Ming Tsao, Akif Turna, Terence Williams.

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Lung Cancer Domain Database. Paula Ugalde (chair), Pietro Bertoglio (co-chair), Sarit Appel, Philippe Joubert, Catherine Labbe, Hongxu Liu, Gustavo Lyons, José-María Matilla, Robert Samstein, Ricardo Terra, Maria Teresa Ruiz Tzukazan, Benny Weksler.

Cancer Research And Biostatistics. Vanessa Cilento, Daniel Dibaba, Megan Eisele, Dorothy Giroux, Emily Goren, Antje Hoering, Katie Nishimura, Adam Rosenthal.

Thymic Epithelial Tumors Domain

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Esophageal Cancer Domain

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Appendix 3. Participating Institutions in the Third Phase of the IASLC Lung Cancer Staging Project

Participating institutions ordered by number of eligible cases submitted

I. Yoshino, Japanese Joint Lung Cancer Registry, Chiba, Japan (23,663 cases); T. Muley, Thoraxklinik, University Hospital Heidelberg, Heidelberg, Germany (8887 cases); W. Li, CAALC: West China Hospital, Sichuan University, Chengdu, People's Republic of China (7345 cases); Y. Kim, Korean Association for Lung Cancer, Seoul, South Korea (4622 cases); H.K. Kim, Samsung Medical Center, Seoul, South Korea (4130 cases); F. Griesinger, CRISP, Berlin, Germany (5482 cases)*; J. Huang, Memorial Sloan Kettering Cancer Center, New York, USA (3146 cases); R. Osarogiagbon, Baptist Memorial Hospital, Memphis, USA (3021cases); S. Park, Seoul National University Hospital, Seoul, South Korea (2542 cases); G. Liu, Princess Margaret Cancer Center, Toronto, Canada (2280 cases); N. Singh, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India (2060 cases); P. Ugalde Figueroa, IUCPQ - Université Laval, Quebec, Canada (2018 cases); P. Kneuertz, The Ohio State University, Columbus, USA (1819 cases); J. Shih, Taiwan Society of Pulmonary and Critical Care Medicine, Taipei, Taiwan (1481 cases); S. Jordan, The Royal Brompton Hospital & E. Beddow, Harefield Hospital, part of Guy's & St. Thomas' NHS Foundation Trust, London, UK (1434 cases); B. McCaughan, University of Sydney, Newtown, Australia (1368 cases); H. Liu, Liaoning Cancer Hospital, Shenyang, Peoples' Republic of China (1161 cases); A. K. Cangir, Ankara University School of Medicine, Ankara-Sihhiye, Turkey (887 cases); A. Billè, Guy's Hospital, London, UK (882 cases); F. Leo, S Luigi Hospital, University of Turin, Orbassano, Torino, Italy (840 cases); H. Liu, Sun Yat-sen University Cancer Center, Guangzhou, People's Republic of China (825 cases); M. Redman, SWOG-0819, Seattle, USA (782 cases); H. Pass, NYU Langone Medical Center and Cancer Center, New York, USA (762 cases); J. Sun, CAALC: Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, People's Republic of China (634 cases); K. Fong, The University of Queensland TPCH Thoracic Research Centre, Brisbane, Australia (577 cases); R. Terra, University of Sao Paulo Medical School, Sao Paulo, Brazil (555 cases); N. Wu, Second Department of Thoracic Surgery, Peking University Cancer, Beijing, People's Republic of China (455 cases); K. Chen, First Department of Thoracic Surgery, Peking University Cancer H, Beijing, People's Republic of China (451 cases); A. Mohan, All India Institute of Medical Sciences, New Delhi, India (448 cases); P. Van Schil, University Hospital Antwerp, Department of Pneumology, Edegem, Belgium (304 cases); P. Bertoglio, IRCCS Sacro Cuore-Don Calabria Hospital, Negrar, Italy (298 cases); C. Yang, Massachusetts General Hospital, Boston, USA (295 cases); R. Moises, Hospital de Rehabilitación Respiratoria María Ferrer, Buenos Aires, Argentina (264 cases); A. Turna, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey (238 cases); A. Celik, Gazi University Faculty of Medicine, Ankara, Turkey (193 cases); M. Modesto Alapont, GCCB3: Consorcio Hospitalario Provincial de Castellón, Castellón, Spain (165 cases); L. Sánchez Moreno and M. Zabaleta Murguiondo, GCCB3: Hospital Universitario Marqués de Valdecilla, Santander, Spain (165 cases); C. Longo, Instituto COI, Rio de Janeiro, Brazil (150 cases); H. Zhou, Suining Central Hospital, Suining, People's Republic of China (147 cases); E. Pirondini, ASST San Gerardo, Monza, Italy (144 cases); G. Lyons, Hospital Británico de Buenos Aires, Buenos Aires, Argentina (143 cases); I. Gkiozos, Athens School of Medicine, Athens, Greece (133 cases); K. Kernstine, UT Southwestern Medical Center at Dallas, Dallas, USA (132 cases); M. Serra Mitjans and R. Costa, GCCB3: Hospital Mútua Terrassa, Barcelona, Spain (124 cases); M. Genovés Crespo and A. Nuñez Ares, GCCB3: Complejo Hospitalario Universitario of Albacete, Albacete, Spain (114 cases); C. Lee, Seoul National University Bundang Hospital, Seongnam, South Korea (104 cases); Y.K. Pang, Malaysian Thoracic Society, Kuala Lumpur, Malaysia (99 cases); N. Evans, Thomas Jefferson University Hospital, Philadelphia, USA (98 cases); F. Hirsch, Icahn School of Medicine at Mount Sinai, New York, USA (84 cases); M. Ridai, University Hospital of Casablanca, Casablanca, Morocco (83 cases); C. Martínez Barenys and J. Sanz Santos, GCCB3: Hospital Universitari Germans Trias i Pujol, Badalona, Spain (77 cases); J. Sauleda Roig, Hospital Universitari Son Espases, Palma de Mallorca, Spain (76 cases); H. Hoffmann, University of Munich - Division of Thoracic Surgery, Munich, Germany (75 cases); M.A.

** CRISP is an AIO study (project no. AIO TRK-0315) under the medical leadership of the Executive Committee (Prof. F. Griesinger [Oldenburg], Prof. M. Thomas [Heidelberg], Dr. M. Sebastian [Frankfurt], and Dr. W. Eberhardt [Essen]). CRISP is conducted by AIO-Studien-gGmbH (sponsor) in cooperation with iOMEDICO (conception, project management, analysis). CRISP is supported by AstraZeneca GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Celgene GmbH, Lilly Deutschland GmbH, Merck Sharp & Dohme GmbH, Novartis Pharma GmbH, Pfizer Pharma GmbH, Roche Pharma AG, and Takeda Pharma Vertrieb GmbH & Co. KG. However, these companies have no input into or influence over data analysis, data interpretation, or writing of the manuscript.*

Iñiguez-García, National Institute of Respiratory Diseases, Mexico City, Mexico (74 cases); L.H. de Lima Araujo, Brazilian National Cancer Institute (INCA), Rio de Janeiro, Brazil (72 cases); C. Grohé, Evangelische Lungenklinik Berlin - NET Registry, Berlin, Germany (71 cases); D. Ball, Peter MacCallum Cancer Institute, Melbourne, Australia (70 cases); J.C. Peñalver Cuesta, GCCB3: Fundación Instituto Valenciano de Oncología, Valencia, Spain (65 cases); N. Tarek, Ain Shams University Hospitals, Cairo, Egypt (64 cases); D. Yang, CAALC: Zhongshan Hospital Fudan University, Shanghai, People's Republic of China (63 cases); D. Sánchez, GCCB3: Hospital Clínic, Barcelona, Spain (62 cases); J.A. Gullón Blanco, GCCB3: Hospital Universitario San Agustín, Avilés, Asturias, Spain (61 cases); L. Montuenga, CIMA/Clínica Universidad de Navarra, Pamplona, Spain (55 cases); G. Galán Gil and R. Guijarro Jorge, GCCB3: Hospital Clínico Universitario de Valencia, Valencia, Spain (52 cases); C. García Rico, J.M. Matilla and B. de Vega Sánchez, GCCB3: Hospital Clínico Universitario de Valladolid, Valladolid, Spain (50 cases); A. Rodríguez Fuster and V. Curall, GCCB3: Hospital del Mar, Barcelona, Spain (50 cases); L. Miravet, GCCB3: Hospital La Plana, Castellón, Spain (49 cases); J. Abal Arca and I. Parente Lamelas, GCCB3: Complexo Hospitalario Universitario Ourense, Ourense, Spain (48 cases); E. Melis, IRCCS Regina Elena National Cancer Institute, Rome, Italy (41 cases); S. García Fuika, GCCB3: Hospital UA Txagorritxu, Vitoria-Gasteiz, Spain (34 cases); K. Tournoy, University Hospital Ghent, Ghent, Belgium (33 cases); M. Zuil Martín, GCCB3: Hospital Royo Villanova, Zaragoza, Spain (31 cases); L. García Aranguena, GCCB3: Hospital Sierrallana, Torrelavega, Cantabria, Spain (28 cases); O. Arrieta, Instituto Nacional de Cancerología, Mexico City, Mexico (28 cases); M. G. Blum, Penrose Cancer Center, Colorado Springs, USA (28 cases); D. Mishra, BP Koirala Institute of Health Sciences, Dharan, Nepal (25 cases); J.M. García Prim, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain (25 cases); M. Mariñán Gorospe, Hospital San Pedro de Logroño, Logroño, Spain (24 cases); R. Stirling, The Alfred Hospital, Melbourne, Australia (23 cases); B. Steen, GCCB3: Hospital de Alcorcón, Madrid, Spain (23 cases); D. Chimondeguy, Hospital Universitario Austral, Buenos Aires, Argentina (22 cases); F.J. Montoro Zulueta, GCCB3: Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain (22 cases); M. Paradela de la Morena and A. Souto Alonso, GCCB3: Complejo Hospitalario Universitario de A Coruña, La Coruña, Spain (21 cases); R. Cordovilla and T. Gómez Hernández, GCCB3: Hospital Universitario de Salamanca, Salamanca, Spain (21 cases); C. Thomas, Mayo Clinic Rochester, Rochester, Minnesota, USA (20 cases); J. Hernández, and I. Lobato Astiárraga, GCCB3: Complejo Asistencial de Ávila, Ávila, Spain (19 cases); I. Macía Vidueira and S. Padrones, GCCB3: Hospital de Bellvitge, Barcelona, Spain (16 cases); J.R. Jarabo Salcedo and B. Morales Chacón, GCCB3: Hospital Clínico San Carlos, Madrid, Spain (16 cases); Y. L. Wu, Guangdong General Hospital, Guangzhou, People's Republic of China (15 cases); E. Martínez Tellez, J.C. Trujillo and V. Pajares Ruiz, GCCB3: Hospital de la Santa Creu i Sant Pau, Barcelona, Spain (14 cases); L. Bai, CAALC: Xinqiao Hospital, No. 3 Army Medical University, Chongqing, People's Republic of China (14 cases); R. Magaroles and L. de Esteban Júlvez, Hospital Universitari Joan XXIII, Tarragona, Spain (14 cases); R. Melchor Íñiguez, Fundación Jiménez Díaz, Madrid, Spain (14 cases); I.R. Embun Flor and P. Teller Justes, GCCB3: Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain (13 cases); C.M. Ariza Prota, GCCB3: Hospital Universitario Asturias, Oviedo, Spain (13 cases); M. J. Pavón Fernández, Hospital Severo Ochoa, Leganés, Spain (13 cases); J. Menéndez, Hospital General de Agudos José M. Penna, Buenos Aires, Argentina (11 cases); S. Defranchi, Hospital Universitario-Fundación Favaloro, Buenos Aires, Argentina (11 cases); E. Martínez Tellez, Hospital de Terrassa, Terrassa, Spain (11 cases).

The following institutions submitted ten eligible cases or less listed alphabetically

M. Curado, A.C. Camargo Cancer Center, Sao Paulo, Brazil; A. Badawy, Alexandria University, Alexandria, Egypt; X. Zhang, CAALC: Henan Provincial People's Hospital, Zhengzhou, People's Republic of China; Q. Wang, CAALC: The Second Hospital of Dalian Medical University, Dalian, People's Republic of China; S. Han, CAALC: Zhongda Hospital Affiliated to Southeast University, Nanjing, People's Republic of China; D. Levy Faber, Carmel Medical Center, Haifa, Israel; P. García Herreros, Clínica Cardiovid, Medellín, Antioquia, Colombia; F. Suárez, Clínica Santa María, Santiago, Chile; D. Subotic, Clinical Center of Serbia, Belgrade, Serbia; T. Horvath, Czech Republic-Urazova nemocnice Brno, BRNO, Czech Republic; M. Velásquez, Fundación Clínica Valle del Lili, Cali, Colombia; T. Ruiz Albi, GCCB3: Hospital Río Hortega, Valladolid, Spain; M. Serraj, Hassan II University Hospital, Fez, Morocco; V. Baysungur, Health Science University Sureyyapasa Thoracic and Chest Disease, Istanbul, Turkey; M. Raíces, Hospital Italiano de Buenos Aires, Argentina; M.J. Pavón Fernández, GCCB3: Hospital Severo Ochoa, Leganés, Madrid, Spain; V. Cvijanovic, Military Medical Academy, Belgrade, Serbia; M. Zereu, Pavilhao Pereira Filho, Santa Casa de Porto Alegre, Brazil; W. Aguiar, SECITOR - Servico de Cirurgia Toracica de Recife, Recife, Brazil.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of*

Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.03.015.

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