

Could tumor spread through air spaces benefit from adjuvant chemotherapy in stage I lung adenocarcinoma? A multi-institutional study

Donglai Chen[#], Xiaofan Wang[#], Fuquan Zhang[#], Ruoshuang Han[#], Qifeng Ding, Xuejun Xu, Jian Shu, Fei Ye, Li Shi, Yiming Mao^{*}, Yongbing Chen^{*}  and Chang Chen^{*}

Abstract

Background: The benefit of adjuvant chemotherapy (ACT) remains unknown for patients with stage I lung adenocarcinoma (ADC) with spread through air spaces (STAS). This study investigated the effect of adjuvant chemotherapy in stage I ADC/STAS-positive patients.

Methods: A total of 3346 patients with stage I ADC from five institutions in China were identified from 2009 to 2013, of whom 1082 were diagnosed with STAS (32.3%). By using the Kaplan–Meier method and Cox proportional hazard regression model, we explored the impact of STAS on prognosis, and determined if the use of adjuvant chemotherapy was associated with improved outcomes in patients with stage I ADC/STAS-positive. A validation cohort was also included in this study.

Results: Patients with stage I ADC/STAS-positive in the primary cohort had unfavorable overall survival (OS) and disease-free survival (DFS). A multivariate Cox regression model confirmed the survival disadvantages of STAS in patients with stage I ADC [OS: hazards ratio (HR)= 1.877, 95% confidence interval (CI): 1.579–2.231; $p < 0.001$; DFS: HR = 1.895, 95% CI: 1.614–2.225; $p < 0.001$]. Lobectomy was associated with better OS and DFS than sublobar resection (SR) in both stage IA and IB ADC/STAS-positive. Similar results were observed in the validation cohort. For patients with stage IB ADC/STAS-positive, ACT was revealed as an independent factor for favorable survival [OS: HR = 0.604, 95% CI: 0.397–0.919; $p = 0.018$; DFS: HR = 0.565, 95% CI: 0.372–0.858; $p = 0.007$]. However, among patients with stage IA ADC/STAS-positive, ACT was associated with improved outcomes only for those undergoing SR [OS: HR = 0.787, 95% CI: 0.359–0.949; $p = 0.034$; DFS: HR = 0.703, 95% CI: 0.330–0.904; $p = 0.029$].

Conclusion: The presence of STAS was correlated with poor prognosis in patients with stage I ADC. Our study suggested that ACT might be considered for patients with stage IB ADC/STAS-positive and those with stage IA ADC/STAS-positive who underwent SR.

Keywords: adjuvant chemotherapy, lung adenocarcinoma, spread through air spaces, surgical procedures, survival

Received: 14 September 2020; revised manuscript accepted: 11 November 2020.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide.¹ Nowadays, surgical resection remains the primary treatment for early-stage non-small cell lung cancer (NSCLC). Although adjuvant chemotherapy (ACT) has been recommended for patients with resected stage II and IIIA NSCLC,²

its role in patients with stage I NSCLC is still inconclusive. Current National Comprehensive Cancer Network guidelines suggest that ACT should be considered in stage IB patients with high-risk factors, including tumor size >4 cm, poorly differentiated lymphovascular invasion, visceral pleura invasion, incomplete lymph node sampling, or

Ther Adv Med Oncol

2020, Vol. 12: 1–13

DOI: 10.1177/
1758835920978147

© The Author(s), 2020.
Article reuse guidelines:
sagepub.com/journals-
permissions

Correspondence to:

Yongbing Chen
Department of Thoracic
Surgery, The Second
Affiliated Hospital of
Soochow University, 1055
Sanxiang Road, Gusu
District, Suzhou, 215004,
China
chentongt@sina.com

Chang Chen
Department of Thoracic
Surgery, Shanghai
Pulmonary Hospital,
Tongji University, School
of Medicine, Shanghai,
200433, China
chenthoracic@163.com

Yiming Mao
Department of Thoracic
Surgery, Suzhou Kowloon
Hospital, Shanghai
Jiaotong University School
of Medicine, Suzhou,
215000, China
253992240@qq.com

Donglai Chen
Department of Thoracic
Surgery, Shanghai
Pulmonary Hospital,
Tongji University, School of
Medicine, Shanghai, China

Xiaofan Wang
Fuquan Zhang
Qifeng Ding
Xuejun Xu
Li Shi

Department of Thoracic
Surgery, The Second
Affiliated Hospital of
Soochow University,
Suzhou, China

Ruoshuang Han
Department of Oncology,
Shanghai Pulmonary
Hospital, Tongji University,
School of Medicine,
Shanghai, China

Jian Shu
Department of Thoracic
Surgery, The Second
Affiliated Hospital of
Soochow University,
Suzhou, China
Department of Thoracic
Surgery, Taicang Affiliated
Hospital of Soochow
University, The First
People's Hospital of
Taicang, Taicang, China

Fei Ye

Department of Thoracic Surgery, The Second Affiliated Hospital of Soochow University, Suzhou, China

Department of Thoracic Surgery, Hai'an Hospital Affiliated to Nantong University, Hai'an, China

#These authors contributed equally.

*Joint co-senior authors.

wedge resection.³ However, whether stage IB patients obtain any survival benefits from ACT is unclear, owing to a lack of robust evidence. In addition, the definition of stage IB disease has been revised in the current 8th TNM staging system,⁴ which highlights the necessity to assess survival benefits from ACT in patients with stage IB NSCLC.

Adenocarcinoma (ADC) is the commonest histologic type of NSCLCs, accounting for approximately 50%.⁵ According to the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society (IASLC/ATS/ERS) classification of 2011, invasive ADC is categorized into several subtypes based on the predominant pattern, including lepidic, acinar, papillary, solid, and micropapillary, as well as invasive mucinous adenocarcinoma.⁶ Hitherto, several studies have reported potential survival advantages of ACT in stage IB patients with high-grade (micropapillary/solid-predominant) ADC.^{7,8} In recent years, tumor spread through air spaces (STAS), has been recognized as a novel invasion pattern in stage I ADCs, which was associated with poor recurrence-free and overall survival.^{9–11} Increasing evidence has revealed a potential relationship between resection types and patient survival in STAS-positive ADC.^{10,12,13} More specifically, lobectomy might offer better outcomes than sublobar resection (SR) in STAS-positive T1 ADC.^{13,14} Besides, our previous study observed that the unfavorable prognosis of patients with stage IA ADC > 2 to 3 cm/STAS-positive was similar to that of patients with stage IB ADC.¹⁴ Nonetheless, there has been no consensus on the use of ACT in stage IA patients with STAS-positive ADC, especially in patients receiving different surgical procedures.

In the present study, we performed a survival analysis using a large multi-institutional cohort to investigate the benefits of ACT for stage IB patients with STAS-positive ADC who underwent different types of resection. We also explored the potential benefits of ACT in patients with stage IA ADC/STAS-positive who underwent SR.

Materials and methods

Patient selection

The Institutional Review Boards of the five hospitals approved this study (IRBNO.JD-HG-2020-09). In cases in which individual patient consent was not identified, the chairpersons of the ethics

committees from the participating institutions waived the need for patient consent. Patients with pT1-2aN0M0 invasive ADC (stage IA and IB) who underwent R0 pulmonary resection at five medical centers in China from January 2009 to December 2013 were reviewed. To exclude distant metastasis, all patients underwent a preoperative routine examination, including enhanced chest computed tomography (CT) scan, enhanced abdominal CT scan or ultrasonography, fiberoptic bronchoscopy, cranial magnetic resonance imaging, and bone scan. A positron emission tomography (PET)-CT scan was suggested if possible. Patients were excluded from the study cohort if one of the following criteria was met: (1) receipt of induction therapy; (2) presence of multiple primary lung cancers; (3) receipt of targeted therapy or immunotherapy; (4) lack of information on lymph nodes status. Platinum-based ACT (cisplatin plus docetaxel or pemetrexed) was performed in patients with high-risk factors including poor differentiated tumor, visceral pleural invasion, vascular invasion, and SR.⁸ Age, performance status, and patients' preference were also considered. No mortality related to chemotherapy was detected among patients who underwent four cycles of ACT. Moreover, we also included a validation cohort (328 patients with stage IA ADC and 251 patients with stage IB ADC) from the Second Affiliated Hospital of Soochow University, with the same criteria, between January 2014 and December 2016.

Histopathologic evaluation of STAS

All specimens were formalin-fixed immediately after resection and stained with hematoxylin and eosin. The slides were reviewed independently by pathologists from respective institutions who were blinded to the patient data. Histological classification was evaluated according to the IASLC/ATS/ERS classification of ADC.⁶ Tumors were classified into lepidic, acinar, papillary, micropapillary, or solid-predominant types when a pattern was predominant in the tumor (even if <50%). The morphological definition of STAS was consistent with that of Travis and Kadota *et al.*,^{15,16} and identification of STAS was described in our previous studies.^{17,18} In brief, lesions of STAS consist of tumor cells that appear morphologically to be situated within normal air spaces as micropapillary clusters, solid nests, or scattered discohesive single cells. In order to avoid confusion with artificially detached cells during tumor dissection, at least three tumor slices were observed under the

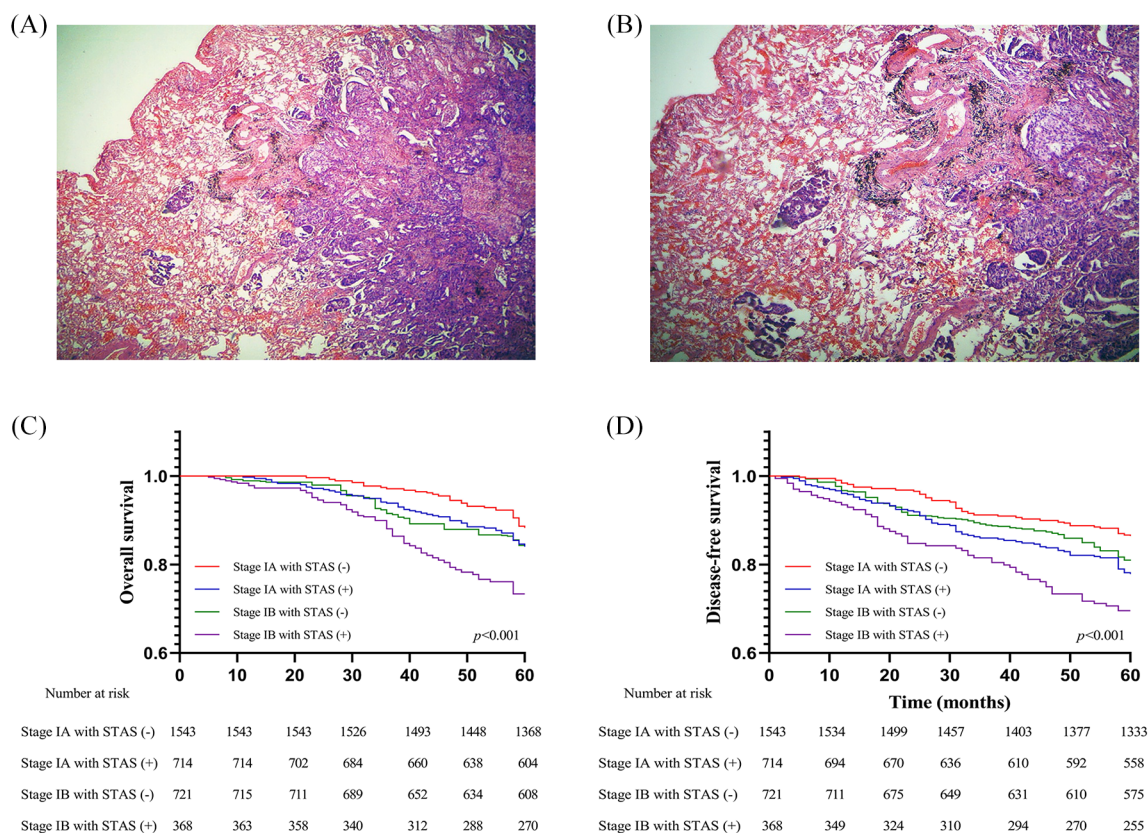


Figure 1. (A) Low-power view and (B) high-power view of tumor spread through air spaces in lung ADC [original magnification: $\times 40$ in A and $\times 100$ in B]; (C) OS, and (D) DFS of patients with stage I ADC stratified by STAS in the primary cohort.

ADC, adenocarcinoma; DFS, disease-free survival; OS, overall survival; STAS, spread through air spaces.

microscope. In addition, distance between the tumor surface and farthest STAS from the tumor edge was measured using a ruler. Because lung specimens were not consistently inflated during processing, to account for artifactual atelectasis, we also measured according to the number of alveolar spaces. Low- and high-power STAS views are shown in Figure 1A,B.

Postoperative follow up

Patients were followed up every 3 months for the first year after surgery and at 6-month intervals thereafter. For patients who were followed up at local health facilities, survival status and examination results were collected by telephone or email. Tumor locoregional recurrence or distant metastasis was diagnosed using chest CT, brain magnetic resonance imaging (MRI), and bone scintigraphy as well as ultrasound and/or abdominal CT. A PET-CT scan was suggested if possible. Disease-free survival (DFS) was defined as

the length of time from surgery to tumor recurrence or the last follow up. Overall survival (OS) was defined as the time from the surgical resection until death from any cause or the last follow up.

Statistical analysis

Associations between clinicopathological characteristics were analyzed using the Pearson χ^2 test or Fisher's exact test for categorical variables. DFS and OS were evaluated using the Kaplan-Meier method, and nonparametric group comparisons were performed using the log-rank test. A Cox proportional-hazards regression model was applied to assess the independent risk factors for DFS and OS. The variables were examined firstly using univariate analyses, and those with p values < 0.1 were incorporated into a multivariate model. Cumulative incidence analysis was used to estimate the cumulative incidence of recurrence (CIR) of locoregional and distant recurrence. All p values were based on two-tailed

statistical analyses, and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (Statistical Program for Social Sciences 25.0; IBM Corporation, Armonk, NY, USA).

Results

Patient clinicopathological characteristics

We identified 3346 and 579 patients with stage I ADC in the primary and validation cohort, respectively. The median number of alveolar spaces between the tumor and the furthest STAS was six in the primary cohort and seven in the validation cohort. In addition, the median distance between tumor surface and the furthest STAS was measured microscopically as 1.3 mm (range, 0.4–6.8 mm) in the primary cohort and 1.1 mm (range, 0.3–7.0 mm).

The detailed clinicopathological characteristics of all patients stratified by STAS and ACT are summarized in Table 1 and Supplemental Table S1. Patients with stage IA ADC accounted for more than 2/3 in the primary cohort, while patients with stage IA ADC took up more than half in the validation cohort. The presence of STAS was found in 1082 ADCs (32.3%) in the primary cohort and 162 ADCs (28.0%) in the validation cohort. Notably, STAS was more likely to be observed in patients with micropapillary-predominant and solid-predominant ADCs in both cohorts. Additionally, the majority of STAS-positive patients underwent lobectomy in both the primary (59.1%) and the validation (64.8%) cohorts. Meanwhile, only a minority of STAS-positive patients received ACT in both cohorts.

The median follow-up time for patients in the primary cohort was 90.8 months, ranging from 80.3 to 139.8 months; while that for patients in the validation cohort was 56.5 months, ranging from 43 to 78 months. The median OS was 65 months (range, 5.4 months to 131.5 months) in the primary cohort and 60 months (range, 8.2 months to 72.7 months) in the validation cohort. Meanwhile, the median DFS was 31 months (range, 1.6 months to 73.5 months) in the primary cohort and 35 months (6.8 months to 63.8 months) in the validation cohort.

STAS affects patient survival in stage I ADC

As shown in Figure 1C–D, survival analysis indicated that patients with STAS suffered from

inferior OS ($p < 0.001$) and DFS ($p < 0.001$) compared with those without STAS in the primary cohort. A similar result was also seen in the validation cohort (Supplemental Figure S1A,B). Notably, it was observed that patients with stage IA ADC/STAS-positive had similar OS (primary cohort: $p = 0.992$; validation cohort: $p = 0.837$) and DFS (primary cohort: $p = 0.202$; validation cohort: $p = 0.923$) to patients with stage IB ADC/STAS-negative in both cohorts (Figure 1 and Supplemental Figure S1). Multivariate Cox regression modeling confirmed the survival disadvantages of STAS in patients with stage I ADC [primary cohort: OS: hazard ratio (HR) = 1.877, 95% confidence interval (CI): 1.579–2.231; $p < 0.001$; DFS: HR = 1.895, 95% CI: 1.614–2.225; $p < 0.001$; Validation cohort: OS: HR = 2.776, 95% CI: 1.658–4.650; $p < 0.001$; DFS: HR = 2.854, 95% CI: 1.727–4.716; $p < 0.001$] in both cohorts (Supplemental Tables S2, S3).

Surgical procedures and ACT affect survival in stage I ADC/STAS-positive patients

Among patients with stage IA ADC/STAS-positive, lobectomy was associated with better OS and DFS than SR, which was observed in both the primary cohort (Figure 2A,B) and in the validation cohort (Supplemental Figure S2A,B). In the multivariate analysis, we further identified lobectomy (OS: HR = 0.509, 95% CI: 0.353–0.733; $p < 0.001$; DFS: HR = 0.470, 95% CI: 0.342–0.647; $p < 0.001$) as an independent predictor of favorable OS and DFS in stage IA ADC/STAS-positive (Table 2). However, ACT was not revealed as an independent factor for favorable survival in patients with stage IA ADC/STAS-positive (OS: HR = 0.696, 95% CI: 0.316–1.534; $p = 0.369$; DFS: HR = 0.550, 95% CI: 0.253–1.197; $p = 0.132$).

Among patients with stage IB ADC/STAS-positive, lobectomy was also associated with advantages in OS and DFS compared with SR, while ACT was associated with additional survival benefits for different types of resection (Figure 2C,D). Notably, lobectomy plus ACT demonstrated the greatest superiority in OS and DFS compared with other treatment modalities. In the multivariate analysis, interestingly, both lobectomy and implementation of ACT were identified as independent predictors of favorable OS and DFS in stage IB ADC irrespective of STAS presence (Table 3). In other words, surgical procedures and ACT could effectively

Table 1. Clinicopathological characteristics of 3346 patients with stage I lung ADC in the primary cohort.

Variables	STAS				Adjuvant chemotherapy			
	No. of patients	Positive (%)	Negative (%)	<i>p</i>	No. of patients	With (%)	Without (%)	<i>p</i>
Overall	3346	1082 (32.3)	2264 (67.7)	<0.001	3346	509 (15.2)	2837 (84.8)	<0.001
Age (years)				0.282				0.283
≤65	2325	657 (28.3)	1668 (71.7)		2325	299 (12.9)	2026 (87.1)	
>65	1021	425 (41.6)	596 (58.4)		1021	210 (20.6)	811 (79.4)	
Sex				0.595				0.881
Male	1854	629 (33.9)	1225 (66.1)		1854	269 (14.5)	1585 (85.5)	
Female	1492	453 (30.4)	1039 (69.6)		1492	240 (16.1)	1252 (83.9)	
Smoking				0.671				0.447
Nonsmoker	1877	542 (28.9)	1335 (71.1)		1877	291 (15.5)	1586 (84.5)	
Current or former smoker	1469	540 (36.8)	929 (63.2)		1469	218 (14.8)	1251 (85.2)	
T stage				<0.001				<0.001
T1a	768	196 (25.5)	572 (74.5)		768	16 (2.1)	752 (97.9)	
T1b	669	236 (35.3)	433 (64.7)		669	29 (4.3)	640 (95.7)	
T1c	820	282 (34.4)	538 (65.6)		820	47 (5.7)	773 (94.3)	
T2a	1089	368 (33.8)	721 (66.2)		1089	417 (38.3)	672 (61.7)	
Histologic pattern				<0.001				<0.001
Lepidic predominant	932	170 (18.2)	762 (81.8)		932	83 (8.9)	849 (91.1)	
Acinar predominant	1003	320 (31.9)	683 (68.1)		1003	125 (12.5)	878 (87.5)	
Papillary predominant	600	198 (33.0)	402 (67.0)		600	91 (15.2)	509 (84.8)	
Micropapillary predominant	256	127 (49.6)	129 (50.4)		256	65 (25.4)	291 (74.6)	
Solid predominant	555	267 (48.1)	288 (51.9)		555	145 (26.1)	410 (73.9)	
Type of surgical resection				0.736				0.869
Thoracotomy	277	132 (47.7)	145 (52.3)		277	108 (39.0)	169 (61.0)	
VATS	3069	950 (31.0)	2119 (69.0)		3069	401 (13.1)	2668 (86.9)	
Surgical procedure				<0.001				<0.001
Lobectomy	1514	640 (42.3)	874 (57.7)		1514	302 (19.9)	1212 (80.1)	
Sublobar resection	1832	442 (24.1)	1390 (75.9)		1832	207 (11.3)	1625 (88.7)	
Presence of STAS					1082	198 (18.3)	884 (81.7)	<0.001

ADC, adenocarcinoma; STAS, spread through air spaces; VATS, video-assisted surgery.

Table 2. Cox proportional-hazards regression model for OS and DFS in patients with stage IA lung ADC in the primary cohort.

Variables	STAS-negative				STAS-positive					
	OS		DFS		OS		DFS			
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis		
<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	
T stage	0.036		0.043	0.090	0.087	0.008	<0.001	0.060	0.003	
T1a		0.658 (0.471–0.920)	0.015	0.717 (0.527–0.976)	0.035	0.457 (0.285–0.734)	0.001	0.516 (0.339–0.784)	0.002	
T1b		0.768 (0.546–1.079)	0.129	0.785 (0.568–1.083)	0.140	0.429 (0.273–0.674)	<0.001	0.614 (0.422–0.894)	0.011	
T1c	1		1		1		1		1	
Histologic Pattern	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
Lepidic predominant		0.636 (0.413–0.979)	0.040	0.719 (0.471–1.097)	0.126	0.256 (0.138–0.472)	<0.001	0.361 (0.216–0.604)	<0.001	
Acinar predominant		0.270 (0.148–0.492)	<0.001	0.517 (0.317–0.844)	0.008	0.491 (0.278–0.869)	0.015	0.545 (0.331–0.899)	0.017	
Papillary predominant		0.647 (0.393–1.066)	0.087	0.913 (0.572–1.455)	0.701	0.582 (0.273–1.244)	0.163	0.645 (0.337–1.235)	0.186	
Micropapillary predominant		1.706 (1.180–2.469)	0.005	1.986 (1.368–2.882)	<0.001	1.007 (0.580–1.747)	0.982	1.006 (0.615–1.646)	0.981	
Solid predominant	1		1		1		1		1	
Surgical Procedure (Lob versus Sublobar)	<0.001	0.838 (0.517–1.359)	0.475	1.103 (0.741–1.642)	0.629	0.509 (0.353–0.733)	<0.001	0.470 (0.342–0.647)	<0.001	
Adjuvant Chemotherapy (with versus without)	<0.001	1.758 (0.992–3.116)	0.053	1.356 (0.734–2.508)	0.331	0.696 (0.316–1.534)	0.369	0.550 (0.253–1.197)	0.132	

ADC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; STAS, spread through air spaces.

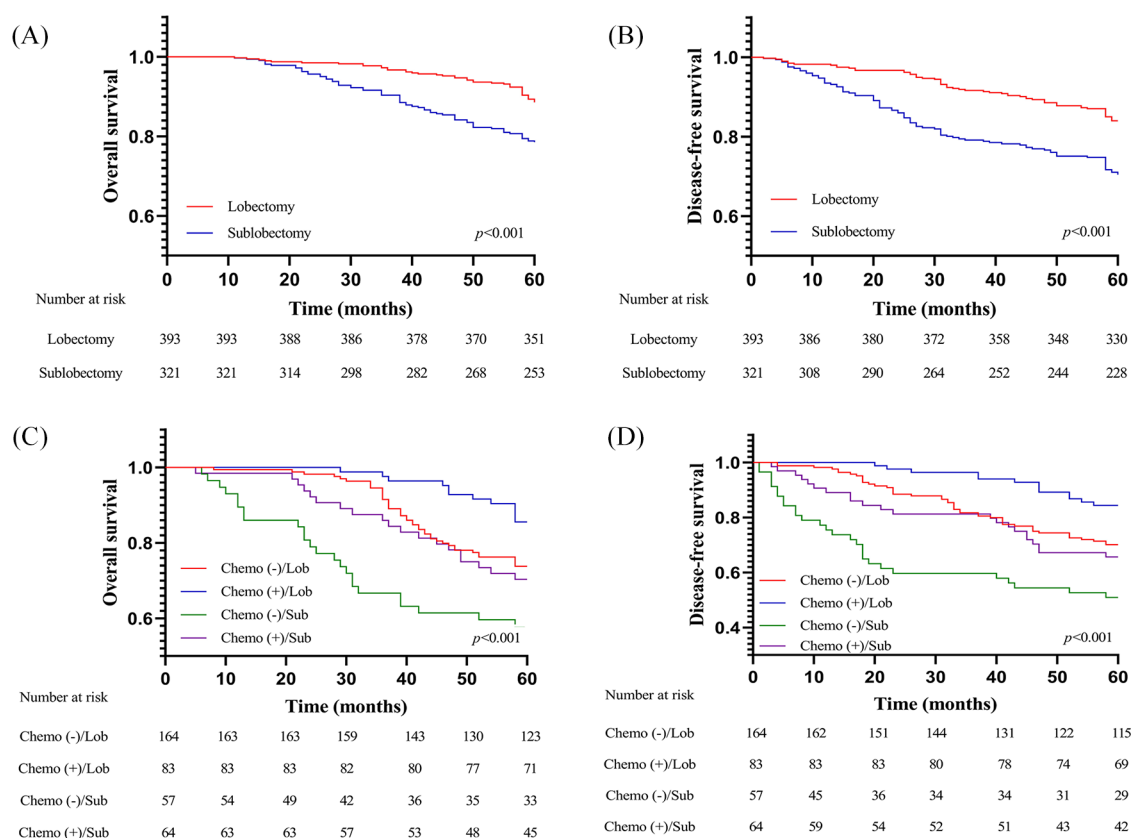


Figure 2. (A) OS and (B) DFS of patients with stage IA ADC/STAS-positive undergoing different surgical procedures in the primary cohort; (C) OS and (D) DFS of patients with stage IB ADC/STAS-positive stratified by surgical procedures and administration of adjuvant chemotherapy in the primary cohort. ADC, adenocarcinoma; DFS, disease-free survival; OS, overall survival; STAS, spread through air spaces.

stratify patient survival in stage IB ADC/STAS-positive.

We further analyzed the types of recurrence in stage IB ADC/STAS-positive. The results revealed that surgical procedures and administration of ACT might be associated with increased risk of developing locoregional ($p=0.022$) and distant ($p<0.001$) recurrence (Supplemental Figure 3A,B). Interestingly, ACT was not associated with significantly decreased locoregional recurrence rate in patients receiving lobectomy ($p=0.184$) and in those receiving SR ($p=0.348$). Notably, lobectomy plus ACT showed significantly lower locoregional recurrence rate compared with SR plus ACT ($p=0.047$). Meanwhile, patients receiving lobectomy alone shared a locoregional recurrence rate similar to those receiving SR plus ACT ($p=0.322$) but had significantly lower locoregional recurrence rate than those receiving SR alone ($p=0.030$). Besides, ACT was associated with decreased distant

recurrence rate in patients undergoing SR ($p=0.035$) and in those undergoing lobectomy ($p=0.023$). It was also observed that lobectomy plus ACT had marginally lower distant recurrence rate than SR plus ACT ($p=0.061$), while lobectomy alone resulted in significantly decreased distant recurrence rate compared with SR alone ($p=0.006$).

Potential benefits of ACT in stage IA ADC/STAS-positive patients

We further performed subgroup analysis on the survival of patients with stage IA ADC/STAS-positive who underwent SR in the primary cohort. As shown in Figure 3A,B, Kaplan–Meier curves revealed that patients with stage IA ADC/STAS-positive receiving ACT after SR had survival advantages compared with those without (OS: $p=0.007$; DFS: $p=0.005$). In multivariate analysis adjusted for age, sex, smoking history, T stage, and histologic subtype, ACT was also indicated

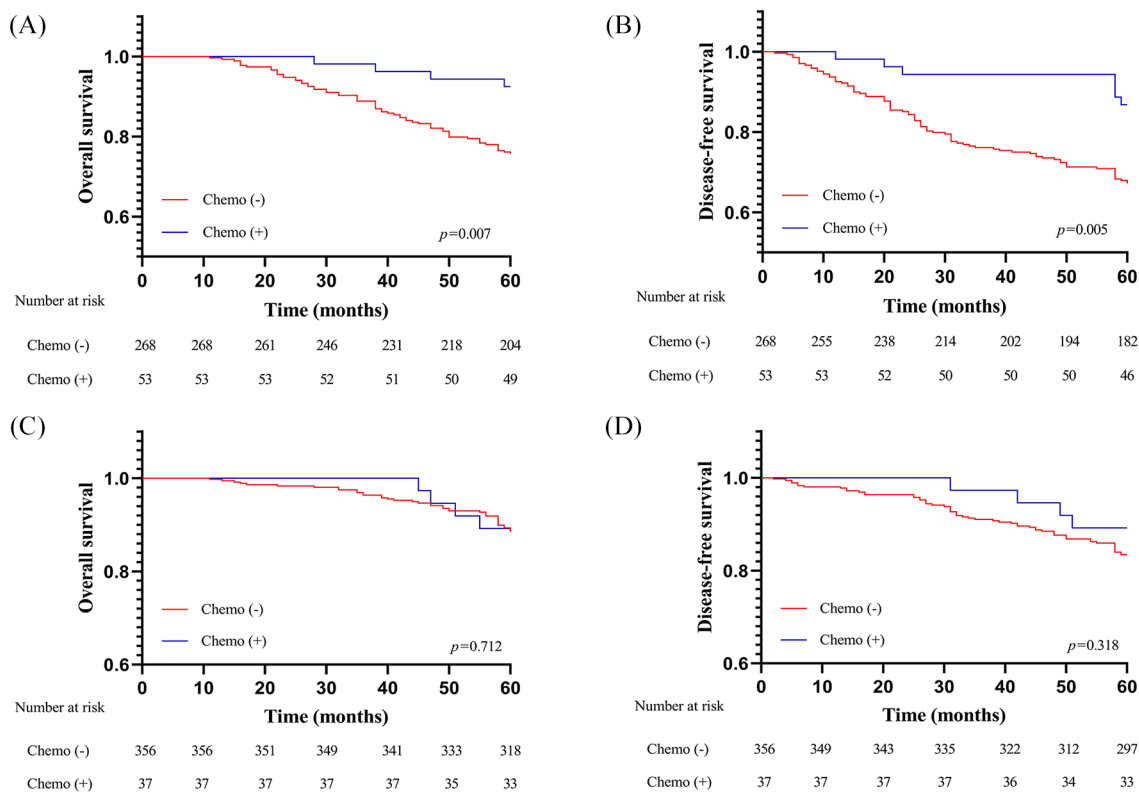


Figure 3. OS and DFS survival of patients with stage IA ADC/STAS-positive receiving SR (A,B) and those receiving lobectomy (C,D) stratified by administration of adjuvant chemotherapy in the primary cohort. ADC, adenocarcinoma; DFS, disease-free survival; OS, overall survival; SR, sublobar resection; STAS, spread through air spaces.

as an independent factor for OS (HR=0.787, 95% CI: 0.359–0.949; $p=0.034$) and DFS (HR=0.703, 95% CI: 0.330–0.904; $p=0.029$) in patients who underwent SR for stage IA ADC/STAS-positive (Supplemental Table S4).

Regarding patients with stage IA ADC/STAS-positive receiving lobectomy, Kaplan–Meier survival analysis indicated that administration of ACT could not provide additional survival benefits (OS: $p=0.712$; DFS: $p=0.318$). Furthermore, it was observed that administration of ACT was not an independent predictor of more favorable OS (HR=0.680, 95% CI: 0.234–1.976; $p=0.479$) and DFS (HR=0.546, 95% CI: 0.193–1.545; $p=0.254$) in patients receiving lobectomy for stage IA ADC/STAS-positive in the multivariate analysis (Supplemental Table S5).

Discussion

Increasing evidence has consistently demonstrated that the presence of STAS in ADCs is

associated with an increased risk of recurrence and a decreased rate of survival.^{10,13,14,19–21} However, no study has assessed the synergistic roles of surgical procedures and adjuvant treatment in stage I ADC patients with pathologically identified STAS. To the best of our knowledge, the present study is the first investigation to offer deep insights into the administration of ACT in stage I ADC/STAS-positive patients.

In our study, we initially confirmed that the presence of STAS remained a robust prognostic factor in both stage IA and IB cohorts. It was noteworthy that stage IA ADC/STAS-positive patients had similar OS and DFS as stage IB ADC/STAS-negative patients. Then, we demonstrated that surgical procedures and ACT could affect survival in stage I ADC/STAS-positive patients. More specifically, lobectomy was associated with better outcomes than SR in both stage IA and IB ADC/STAS-positive patients, while administration of ACT was an independent predictor of favorable survival only in stage IB ADC/

Table 3. Cox proportional-hazards regression model for OS and DFS in patients with stage IB lung ADC in the primary cohort.

Variables	STAS-negative						STAS-positive					
	OS			DFS			OS			DFS		
	Univariate analysis	Multivariate analysis	HR (95% CI)	p	Univariate analysis	Multivariate analysis	HR (95% CI)	p	Univariate analysis	Multivariate analysis	HR (95% CI)	p
Histologic Pattern	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.017	<0.001	<0.001	0.003
Lepidic predominant		0.375 [0.196-0.720]	0.003	0.389 [0.201-0.751]	0.005	0.784 [0.409-1.503]	0.464	0.816 [0.431-1.545]	0.533			
Acinar predominant		0.421 [0.234-0.756]	0.004	0.432 [0.239-0.780]	0.005	0.825 [0.446-1.523]	0.538	0.831 [0.443-1.558]	0.563			
Papillary predominant		0.260 [0.117-0.577]	0.001	0.750 [0.426-1.321]	0.319	0.940 [0.507-1.741]	0.844	0.945 [0.506-1.766]	0.859			
Micropapillary predominant		1.607 [0.993-2.600]	0.053	1.870 [1.154-3.030]	0.011	1.831 [1.039-3.228]	0.037	2.044 [1.157-3.609]	0.014			
Solid predominant		1		1		1		1				
Surgical Procedure (Lob versus Sublobar)	<0.001	0.482 [0.340-0.685]	<0.001	0.588 [0.422-0.819]	0.002	0.476 [0.323-0.702]	<0.001	0.468 [0.319-0.688]	<0.001			
Adjuvant Chemotherapy (with versus without)	0.002	0.559 [0.368-0.850]	0.006	0.463 [0.309-0.693]	<0.001	0.604 [0.397-0.919]	0.018	0.565 [0.372-0.858]	0.007			

ADC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; STAS, spread through air spaces.

STAS-positive patients. In terms of patients receiving SR for a stage IA ADC/STAS-positive diagnosis, ACT was revealed as an independent predictor of improved survival. Interestingly, administration of ACT did not bring additional survival benefits in stage IA ADC/STAS-positive patients receiving lobectomy.

In recent years, an increasing number of studies have assessed potential candidates with stage IA ADC who might benefit from ACT.^{22–25} It has been reported that ACT might improve outcomes after resection of stage IA ADC with lymphovascular invasion, which is another invasion pattern of ADC in addition to STAS. Liu *et al.* proposed that poor differentiation is an independent prognostic factor in pathological stage IA ADC after surgical resection.²² Recently, Wang *et al.* also confirmed the survival advantages of ACT for patients with micropapillary-predominant pattern in stage IA.²⁴ Notably, STAS was found significantly associated with high-grade histological patterns including solid- and micropapillary-predominant subtypes in previous studies.^{10,26,27} Therefore, we further confirmed administration of ACT as a predictor of favorable OS in stage I/STAS-positive patients irrespective of micropapillary or solid component presence (Supplemental Table S6). Additionally, it has been revealed that STAS could be observed in residual lung segments after SR for stage IA disease.¹² Taken together, it was reasonable to observe that ACT brought improved survival to stage IA ADC/STAS-positive patients receiving SR rather than those receiving lobectomy.

A number of studies have investigated different approaches to identify STAS in ADCs pre- and intraoperatively.^{13,19,28–31} To name just a few, Toyokawa *et al.* reported that the presence of notch and the absence of ground-glass opacity (GGO) were associated significantly with STAS in ADCs.²⁹ Such findings were supported by Kim *et al.*, who observed that STAS was also associated with central low attenuation, ill-defined opacity, air bronchogram, and large percentage of solid component.³⁰ Our previous study proved that radiomics-based prediction using machine learning was also a promising approach to identify STAS preoperatively, which was supported by Zhuo *et al.* and Jiang *et al.*^{28,32} Recently, Suh *et al.* developed a step-wise flowchart for decision making on SR through the estimation of STAS consisting of both preoperative radiological features and

intraoperative frozen pathology, which displayed good performance.³³ In terms of frozen pathology, Eguchi *et al.* found that, in patients with T1 ADC, identifying STAS in frozen sections could be feasible with proved acceptable sensitivity and high specificity.¹³ Besides, it has been reported that intraoperative imprint cytology with the N–H classification for ADC was well correlated with the STAS status of the tumor.³⁴ Therefore, mounting methods have emerged to allow the precise detection of STAS, which will be helpful in the decision-making process for surgical procedures.

We have to acknowledge some limitations of our study. First, the retrospective nature of our multicenter study might lead to selection and performance bias. Second, the number of STAS-positive patients was limited in the validation cohort, especially those receiving SR or ACT, which resulted in the unavailability of external validation of the potential benefits of ACT in stage IA ADC/STAS-positive cohorts. Third, there have been controversies as to whether any part of the free-floating tumor cell clusters identified as STAS are actually *ex vivo* artifacts. The most notable is the possibility that the tumor cell clusters can be spread through knife cuts made at the time of specimen processing, named as “spread through a knife surface” (STAKS).³⁵ Although at least three tumor slices were observed under the microscope for each specimen, it was inevitable for us to include patients with STAKS rather than true STAS. By the way, we did not assess the relationship between STAS morphology and ACT benefit because of the limited number of STAS-positive patients who underwent ACT in both cohorts. Additionally, ACT decision and regimen selection were based on subjective preference rather than randomization.

In conclusion, the presence of STAS is correlated with poor prognosis in patients with stage I ADC. ACT is a favorable prognostic factor for stage IB ADC/STAS-positive patients. ACT improves outcomes in stage IA ADC/STAS-positive patients who underwent SR, whereas it provides no additional survival benefits for stage IA ADC/STAS-positive patients receiving lobectomy.

Acknowledgements

The authors thank the patients and the study staff of the five medical centers for their contributions to our research. We would like to thank Huikang

Xie (Department of Pathology, Tongji University Affiliated Shanghai Pulmonary Hospital), Yongsheng Zhang (Department of Pathology, the Second Affiliated Hospital of Soochow University), Guojian Gu (the First People's Hospital of Taicang), Guiyuan Gu (Hai'an Hospital Affiliated to Nantong University), and Xiang Jiang (Department of Pathology, Suzhou Kowloon Hospital Shanghai Jiaotong University School of Medicine) for their help with reviewing the slides.

Author contributions

Conception and design: DC, XW, FZ and RH;

Acquisition of data: DC, XW, QD, JS, FY, LS, YM.

Analysis and interpretation of data: DC, XW, FZ, RH and XX.

Drafting of the manuscript: DC, XW, FZ, RH, QD and XX.

Critical revision of the manuscript for important intellectual content: LS, YM, JS and FY.

Supervision and acquisition of the funding: CC and YC.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the projects from Suzhou Key Laboratory of Thoracic Oncology (SZS201907), Suzhou Key Discipline for Medicine (SZXK201803), Municipal Program of People's Livelihood Science and Technology in Suzhou (SS2019061) and Jiangsu Key Research and Development Plan (Social Development) Project (BE2020653).

ORCID iD

Yongbing Chen  <https://orcid.org/0000-0002-7595-092X>

Availability of data and materials

Data is available upon reasonable request.

Supplemental material

Supplemental material for this article is available online.

References

1. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424.
2. Kris MG, Gaspar LE, Chaft JE, *et al.* Adjuvant systemic therapy and adjuvant radiation therapy for stage I to IIIa completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario clinical practice guideline update. *J Clin Oncol* 2017; 35: 2960–2974.
3. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines): non-small cell lung cancer, version 6. 2020. <https://www.nccn.org/patients/guidelines/cancers.aspx#nslc>. (2020, accessed 15 June 2020)
4. Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 39–51.
5. Warth A, Muley T, Meister M, *et al.* The Novel Histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. *J Clin Oncol* 2012; 30: 1438–1446.
6. Travis WD, Brambilla E, Noguchi M, *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6: 244–285.
7. Qian F, Yang W, Wang R, *et al.* Prognostic significance and adjuvant chemotherapy survival benefits of a solid or micropapillary pattern in patients with resected stage IB lung adenocarcinoma. *J Thorac Cardiovasc Surg* 2018; 155: 1227–1235.e2.
8. Ma M, She Y, Ren Y, *et al.* Micropapillary or solid pattern predicts recurrence free survival benefit from adjuvant chemotherapy in patients with stage IB lung adenocarcinoma. *J Thorac Dis* 2018; 10: 5384–5393.
9. Adusumilli PS. Spread through alveolar spaces: an aerogenous invasion in pulmonary adenocarcinomas. *J Thorac Cardiovasc Surg* 2016; 152: 73–74.
10. Chen D, Mao Y, Wen J, *et al.* Tumor spread through air spaces in non-small cell lung cancer: a

- systematic review and meta-analysis. *Ann Thorac Surg* 2019; 108: 945–954.
11. Wang S, Hao J, Qian C, *et al.* Tumor spread through air spaces is a survival predictor in non-small-cell lung cancer. *Clin Lung Cancer* 2019; 20: e584–e591.
 12. Ren Y, Xie H, Dai C, *et al.* Prognostic impact of tumor spread through air spaces in sublobar resection for 1a lung adenocarcinoma patients. *Ann Surg Oncol* 2019; 26: 1901–1908.
 13. Eguchi T, Kameda K, Lu S, *et al.* Lobectomy is associated with better outcomes than sublobar resection in Spread Through Air Spaces (STAS)-positive T1 lung adenocarcinoma: a propensity score matched analysis. *J Thorac Oncol*. Epub ahead of print 19 September 2018. DOI: 10.1016/j.jtho.2018.09.005.
 14. Dai C, Xie H, Su H, *et al.* Tumor spread through air spaces affects the recurrence and overall survival in patients with lung adenocarcinoma >2 to 3 cm. *J Thorac Oncol* 2017; 12: 1052–1060.
 15. Travis WD, Brambilla E, Nicholson AG, *et al.* The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015; 10: 1243–1260.
 16. Kadota K, Nitadori J, Sima CS, *et al.* Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. *J Thorac Oncol* 2015; 10: 806–814.
 17. Ding Q, Chen D, Wang X, *et al.* Characterization of lung adenocarcinoma with a cribriform component reveals its association with spread through air spaces and poor outcomes. *Lung Cancer* 2019; 134: 238–244.
 18. Liu Y, Chen D, Qiu X, *et al.* Relationship between MTA1 and spread through air space and their joint influence on prognosis of patients with stage I-III lung adenocarcinoma. *Lung Cancer* 2018; 124: 211–218.
 19. Chen D, She Y, Wang T, *et al.* Radiomics-based prediction for tumour spread through air spaces in stage I lung adenocarcinoma using machine learning. *Eur J Cardiothorac Surg* 2020; 58: 51–58.
 20. Vaghjiani RG, Takahashi Y, Eguchi T, *et al.* Tumor spread through air spaces is a predictor of occult lymph node metastasis in clinical stage IA lung adenocarcinoma. *J Thorac Oncol* 2020; 15: 792–802.
 21. Toki MI, Harrington K and Syrigos KN. The role of Spread Through Air Spaces (STAS) in lung adenocarcinoma prognosis and therapeutic decision making. *Lung Cancer* 2020; 146: 127–133.
 22. Liu CH, Peng YJ, Wang HH, *et al.* Heterogeneous prognosis and adjuvant chemotherapy in pathological stage I non-small cell lung cancer patients. *Thorac Cancer* 2015; 6: 620–628.
 23. Woodard GA, Wang SX, Kratz JR, *et al.* Adjuvant chemotherapy guided by molecular profiling and improved outcomes in early stage, non-small-cell lung cancer. *Clin Lung Cancer* 2018; 19: 58–64.
 24. Wang C, Yang J and Lu M. Micropapillary predominant lung adenocarcinoma in stage IA benefits from adjuvant chemotherapy. *Ann Surg Oncol* 2020; 27: 2051–2060.
 25. Wang S, Xu J, Wang R, *et al.* Adjuvant chemotherapy may improve prognosis after resection of stage I lung cancer with lymphovascular invasion. *J Thorac Cardiovasc Surg* 2018; 156: 2006–2015.e2.
 26. Lee JS, Kim EK, Kim M, *et al.* Genetic and clinicopathologic characteristics of lung adenocarcinoma with tumor spread through air spaces. *Lung Cancer* 2018; 123: 121–126.
 27. Masai K, Sakurai H, Sukeda A, *et al.* Prognostic impact of margin distance and tumor spread through air spaces in limited resection for primary lung cancer. *J Thorac Oncol* 2017; 12: 1788–1797.
 28. Jiang C, Luo Y, Yuan J, *et al.* CT-based radiomics and machine learning to predict spread through air space in lung adenocarcinoma. *Eur Radiol* 2020; 30: 4050–4057.
 29. Toyokawa G, Yamada Y, Tagawa T, *et al.* Computed tomography features of resected lung adenocarcinomas with spread through air spaces. *J Thorac Cardiovasc Surg* 2018; 156: 1670–1676.e4.
 30. Kim SK, Kim TJ, Chung MJ, *et al.* Lung adenocarcinoma: CT features associated with spread through air spaces. *Radiology* 2018; 289: 831–840.
 31. Walts AE and Marchevsky AM. Current evidence does not warrant frozen section evaluation for the presence of tumor spread through alveolar spaces. *Arch Pathol Lab Med* 2018; 142: 59–63.
 32. Zhuo Y, Feng M, Yang S, *et al.* Radiomics nomograms of tumors and peritumoral regions for the preoperative prediction of spread through air spaces in lung adenocarcinoma. *Transl Oncol* 2020; 13: 100820.

33. Suh JW, Jeong YH, Cho A, *et al.* Stepwise flowchart for decision making on sublobar resection through the estimation of spread through air space in early stage lung cancer. *Lung Cancer* 2020; 142: 28–33.
34. Kimura T, Nakamura H, Omura A, *et al.* Novel imprint cytological classification is correlated with tumor spread through air spaces in lung adenocarcinoma. *Lung Cancer* 2020; 148: 62–68.
35. Blaauwgeers H, Flieder D, Warth A, *et al.* A prospective study of loose tissue fragments in non-small cell lung cancer resection specimens: an alternative view to “spread through air spaces”. *Am J Surg Pathol* 2017; 41: 1226–1230.

Visit SAGE journals online
[journals.sagepub.com/
home/tam](https://journals.sagepub.com/home/tam)

 SAGE journals