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Characterization of lung adenocarcinoma with a cribriform component reveals its association with spread through air spaces and poor outcomes

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ABSTRACT

Objective: To further investigate the relationship between the cribriform component and spread through air spaces (STAS), and to unravel the potential pathological mechanism of poor prognoses in lung adenocarcinoma (LUAD) patients with a cribriform component.

Methods: We retrospectively reviewed the clinicopathological characteristics of 208 LUADs. The cribriform component was identified by hematoxylin and eosin staining. The identification of STAS referred to our previous study. The relationship between the cribriform component and STAS was determined by using a logistic regression model. The effects of the cribriform component and STAS on prognosis were analyzed using a Cox proportional hazards regression model.

Results: LUAD patients with a cribriform component had significantly inferior outcomes and increased risk of both locoregional and distant recurrences when compared with those with no cribriform component ($p < 0.001$). Among 67 patients with a cribriform component presented, 48 (71.6%) cases had STAS. The logistic regression model identified that the cribriform component was an independent risk factor for the presence of STAS ($p = 0.044$). Subgroup analysis showed that Crib+ (cribriform component present)/STAS+ (spread through air spaces positive) patients had significantly inferior outcomes when compared with Crib+/STAS- (spread through air spaces negative) patients ($p < 0.001$). Moreover, the multivariate Cox regression analysis further confirmed that STAS was an independent risk factor for a worsening recurrence-free survival (RFS) ($p = 0.001$) and overall survival (OS) ($p < 0.001$) in LUAD patients with a cribriform component.

Conclusions: Our results indicated that STAS was more frequently observed in LUAD patients with a cribriform component. Moreover, STAS could provide helpful prognostic information in patients with stage I-III LUAD with a cribriform component.

1. Introduction

Lung cancer is the most common cause of cancer related mortality worldwide [1,2]. At present, adenocarcinoma is the most common histological type of lung cancer [3]. In 2011, a new multidisciplinary classification for lung adenocarcinoma (LUAD) was proposed by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society, which classified lung invasive adenocarcinoma into five main pathological subtypes, including: acinar, solid, micropapillary, papillary, and lepidic [4]. Among the five pathological subtypes, the acinar-predominant subtype accounts for the highest percentage [5,6], and this subtype demonstrates significant heterogeneity in prognosis [7]. One of the main reasons for different prognoses seen with acinar-predominant LUAD is related to histological heterogeneity [8]. According to the 2015 World Health Organization (WHO) classification of the lung cancer, a distinctive histological pattern named cribriform component, which has been included in acinar-predominant adenocarcinoma [9]. Several

Abbreviations: STAS, spread through air spaces; LUAD, lung adenocarcinoma; Crib+, cribriform component present; Cri, b-cribriform component absent; STAS+, spread through air spaces positive; STAS-, spread through air spaces negative; RFS, recurrence-free survival; OS=, overall survival

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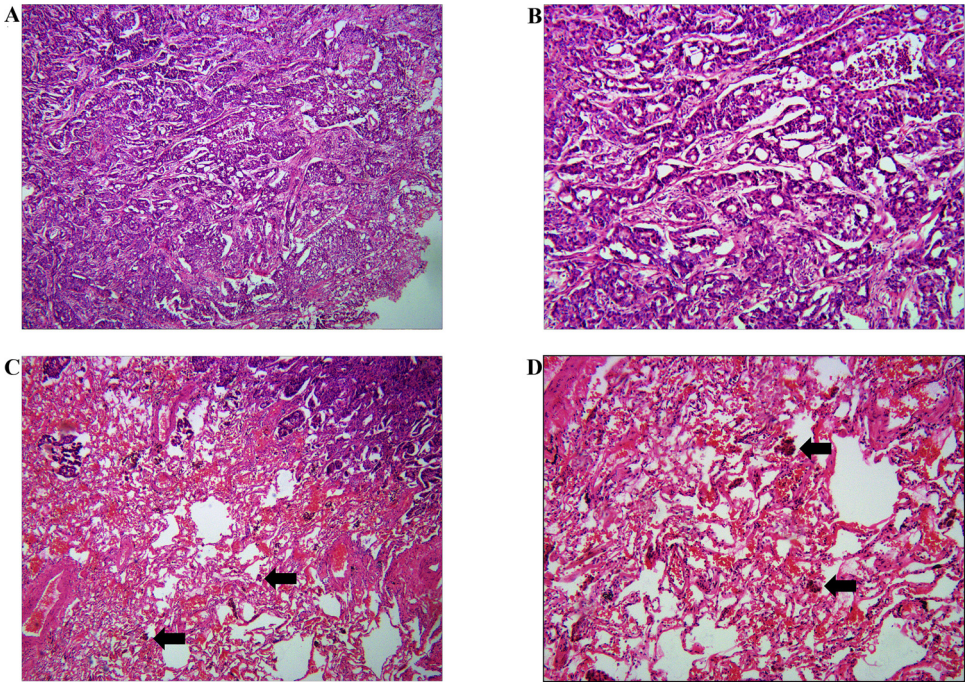


Fig. 1. Microscopic features of the cribriform component and spread through air spaces (STAS). A, Low-power view of the cribriform component; B: High-power view of the cribriform component. C, Low-power view of STAS; D: High-power view of STAS.

studies have demonstrated that the cribriform component may further stratify survival in acinar-predominant LUADs [10–14].

In a previous study, Xu et al. [15] demonstrated that the cribriform component could have a high rate of lymph node metastasis. Kadota and colleagues [10] reported that the presence (≥10%) of the cribriform component correlated with smoking history, higher stage disease, and pleural invasion. Moreover, the authors revealed that the cribriform component (≥10%) can stratify acinar-predominant tumors with respect to recurrence and may be an independent risk factor for recurrence in stage I LUADs. Warth et al. [11] confirmed that patients with cribriform predominant tumors had the least favorable outcomes for disease-free survival after reviewing 674 resected LUADs with stage I-IV disease. However, such studies have seldom investigated the likely pathological mechanism of the association between LUAD with a cribriform component and poor outcome.

Along with the publication relating to the WHO classification of lung cancer in 2015 [9], several new morphological features have been proposed that might be prognostically significant. Besides the cribriform component, spread through air spaces (STAS) is one such feature [16], and has captured attention in recent studies. Warth et al. [17] declared that the presence of STAS was identified in nearly half of 569 LUAD patients with surgical resections. Kadota et al. [16] found that patients with positive STAS who accepted limited resection had higher risks of recurrence than those with negative STAS. Our previous study has shown that the STAS-positive status was significantly associated with poor survival in patients irrespective of surgical procedures [18], which was consistent with other studies [19–22].

To further investigate the relationship between the cribriform component and STAS, and to unravel a potential pathological mechanism of the poor prognosis due to the cribriform component, we analyzed a cohort of 208 patients with surgically resected LUADs.

2. Materials and methods

2.1. Patients

In the present study, we retrospectively reviewed 312 patients with invasive LUADs who underwent surgical resection in the Second Affiliated Hospital of Soochow University from January 2009 to December 2014. The patients enrolled in our research had to meet the following inclusion criteria: (1) patients without preoperative neoadjuvant treatment, and (2) patients pathologically diagnosed with primary T1-4N0-2M0 adenocarcinoma (stage I-III) based on the eighth edition of the American Joint Committee on Cancer TNM Staging Manual [23]. The exclusion criterion was as follows: (1) patients who were lost to a follow-up and (2) patients with simultaneous multiple tumors or other primary malignancies. According to these criteria, 42 patients who experienced preoperative neoadjuvant radiochemotherapy and 62 patients who were lost to a follow-up were excluded, whereas the remainder of 208 patients were included. Clinical data including sex, age, smoking history, lymph node status etc, were acquired from the lung cancer database in our department. Disease recurrence was confirmed by clinical, radiological, or pathological diagnosis. Informed consent from the patients was waived because of the retrospective nature of this study.

2.2. Histopathologic evaluation

All specimens were formalin fixed immediately after resection and stained with hematoxylin and eosin. The slides were reviewed independently by two pathologists (YS. Z. and F. L) who were blinded to the patient data. Histological classification was evaluated according to the 2015 WHO classification of lung tumors [9]. The cribriform component was defined as invasive back-to-back fused tumor glands with poorly formed glandular spaces lacking intervening stroma or invasive tumor nests of tumors cells that produce glandular lumina without solid components (Fig. 1), which was in accordance with Kadota et al [10]. The proportion of each histological component (lepidic component, acinar component, papillary component, micropapillary component, solid component and cribriform component) was recorded in 5% increments and was considered to be present when observed for ≥ 5% in a case.

The morphological definition of STAS was consistent with that of Travis and Kadota [9,16], and the identification of STAS is described in our previous study [18] as shown in Fig. 1.

2.3. Statistical methods

Associations between clinicopathological characteristics were analyzed using the Pearson χ^2 test or Fisher's exact test for categorical variables. In addition, the logistic regression model was applied to confirm the independent risk factors for the presence of STAS. Recurrence-free survival (RFS) was defined as the time from the surgical resection to the first time of recurrence. Overall survival (OS) was defined as the time from the surgical resection until death from any cause or last follow-up. RFS 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 RFS and OS. The variables were examined firstly using univariate analyses, and those with p-values < 0.05 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).

3. Results

3.1. Clinicopathological characteristics and patient outcome

Clinicopathological variables for all 208 patients were obtained and listed in Table 1. The median age of patients at diagnosis was 65 years (range, 31–81 years). More than half of the patients were men (n = 108). In total, 44% of the patients were current smokers or former smokers, and 56% were non-smokers. Surgically, 154 patients underwent lobectomy or more, and others underwent limited resection (segmentectomy or wedge resection), accompanied by systematic lymph node dissection in half of the cases (50.5%). Stage distribution of the enrolled cases was based on the 8th edition of the Cancer Staging System [23] and was as follows (n): stage I (86), stage II (77), stage III (45).

During the follow-up, recurrence was observed in 100 patients, and death was reported in 123. The median follow-up time of the patients alive at the point of last follow-up was 56 months.

3.2. Histological distribution

Of all cases, counting the cribriform component as acinar pattern, the distribution of the five pathological subtypes was as follows: 96 (46%) cases with an acinar predominant subtype, 66 (32%) cases with a papillary predominant subtype, 29 (14%) cases with a solid predominant subtype, 9 (4%) cases with a lepidic predominant subtype, and 8 (4%) cases with a micropapillary predominant subtype. In terms of the present growth pattern (≥5%), 168 tumors (81%) had multiple patterns, and 40 tumors had just one. We found 127 of the cases with an acinar component, 103 with a papillary component, 76 with a solid component, 58 with a lepidic component, 39 with a micropapillary component, and 67 cases with a cribriform component.

The frequency of the cribriform component was highest in tumors with a solid component (46 of 76, 60.5%), followed by tumors with an acinar component (30 of 127, 23.6%), then tumors with a micropapillary component (26 of 45, 57.8%), papillary component (25 of 103, 24.3%), and finally in tumors with a lepidic component (1 of 58, 1.7%).

In addition, 107 patients were diagnosed with the STAS-positive status (Table 1).

3.3. Prognostic impact of the cribriform component

After the type of recurrence in all patients was analyzed, the results revealed that patients with a cribriform component had a significantly increased risk of developing locoregional recurrences when compared with those in the absence of a cribriform component (5-year CIR, 57% vs. 20%, $p < 0.001$; Fig. 2). Furthermore, patients with a cribriform component also had a significantly increased risk of developing distant recurrences compared with those in the absence of a cribriform

Table 1
Clinicopathological Characteristics of 208 Patients with Stage I-III Lung Adenocarcinoma.

Variables	No. of patients	Cribriform component			No. of patients	STAS		
		Present(%)	Absent(%)	p		Positive(%)	Negative(%)	p
Overall	208	67(32.2)	141(67.8%)		208	107(51.4)	101(48.6)	
Age(y)				0.696				0.727
≤65	86	29(33.7)	57(66.3)		86	43(50.0)	43(50.0)	
> 65	122	38(31.1)	84(68.9)		122	64(52.5)	58(47.5)	
Sex				0.065				0.217
Male	108	41(38.0)	67(62.0)		108	60(55.6)	48(44.4)	
Female	100	26(26.0)	74(74.0)		100	47(47.0)	53(53.0)	
Smoking				0.002				0.851
Nonsmoker	116	27(23.3)	89(76.7)		116	59(50.9)	57(49.1)	
Current or former smoker	92	40(43.5)	52(56.5)		92	48(52.2)	44(47.8)	
pT				< 0.001				0.003
T1	103	19(18.4)	84(81.6)		103	40(38.8)	63(61.2)	
T2	84	32(38.1)	52(61.9)		84	52(61.9)	32(38.1)	
T3	16	12(75.0)	4(25.0)		16	11(68.8)	5(31.2)	
T4	5	4(80.0)	1(20.0)		5	4(80.0)	1(20.0)	
pN				< 0.001				< 0.001
N0	111	11(9.9)	100(90.1)		111	45(40.5)	66(59.5)	
N1	64	32(50.0)	32(50.0)		64	36(56.3)	28(43.7)	
N2	33	24(72.7)	9(27.3)		33	26(78.8)	7(21.2)	
Histologic component								
Lepidic component	58	1(1.7)	57(98.3)	< 0.001	58	25(43.1)	33(56.9)	0.135
Acinar component	127	30(23.6)	97(76.4)	0.001	127	63(49.6)	64(50.4)	0.507
Papillary component	103	25(24.3)	78(75.7)	0.015	103	48(46.6)	55(53.4)	0.167
Solid component	76	46(60.5)	30(39.5)	< 0.001	76	46(60.5)	30(39.5)	0.047
Micropapillary component	45	26(57.8)	19(42.2)	0.039	45	29(64.4)	16(35.6)	0.049
Presence of STAS	107	48(44.9)	59(55.1)	< 0.001				

No., number; *pT*, pathological tumor stage; *pN*, pathological lymph node stage; *STAS*, spread through air spaces.

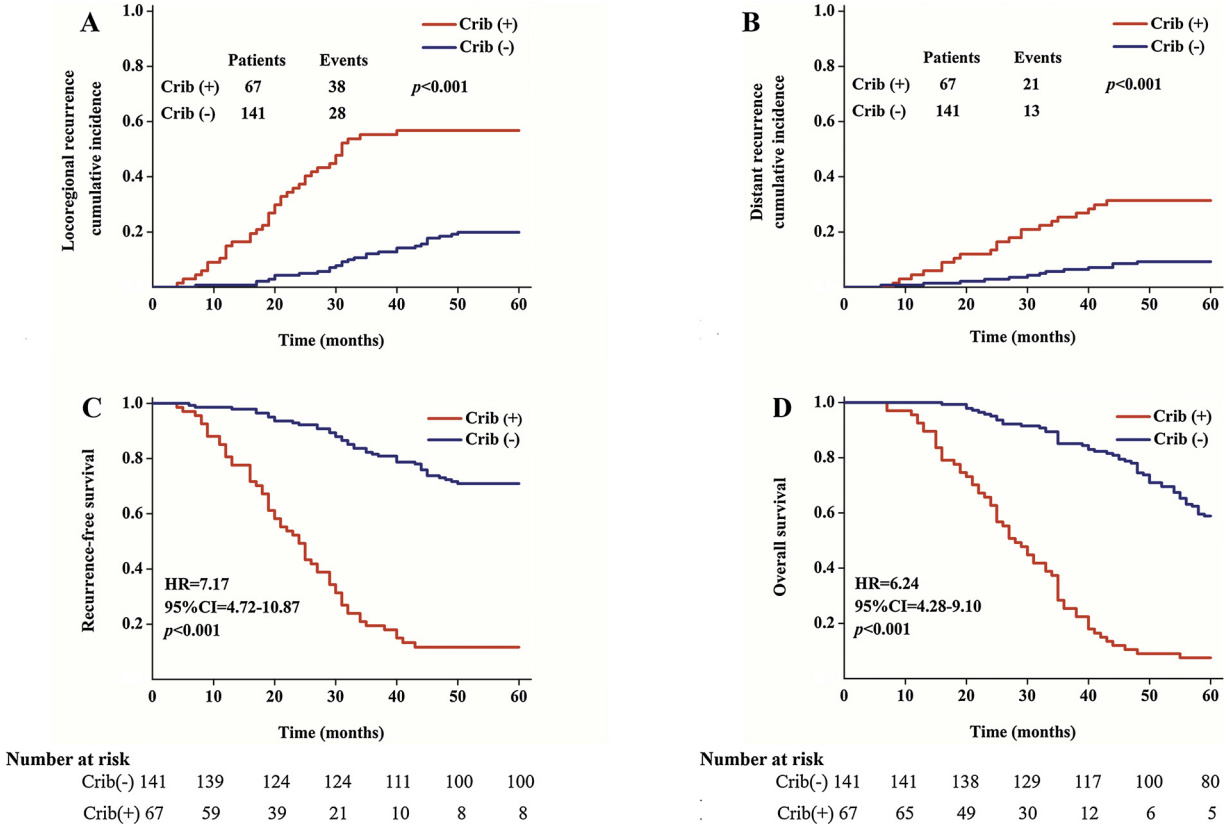


Fig. 2. Cumulative incidence of locoregional recurrence (A) and distant recurrence (B) in patients with stage I-III lung adenocarcinoma stratified by the cribriform component. Recurrence-free survival (C) and overall survival (D) in patients with stage I-III lung adenocarcinoma stratified by the cribriform component. *Crib* (+): cribriform component present, *Crib* (-): cribriform component absent; *HR*, hazard ratio; *CI*, confidence interval.

component (5-year CIR, 31% vs. 9%, $p < 0.001$; Fig. 2).

The log-rank tests indicated that patients presenting with a cribriform component had significantly inferior RFS (5-year rate: 12% vs. 71%, $p < 0.001$) and OS (5-year rate: 8% vs. 56%, $p < 0.001$) compared with those in the absence of a cribriform component (Fig. 2). In addition, multivariate analyses confirmed that both the cribriform component (hazard ratio [HR] of RFS, 2.82, 95% confidence interval [CI], 1.68–4.74, $p < 0.001$; HR of OS, 2.73, 95% CI, 1.74–4.29, $p < 0.001$) and STAS (HR of RFS, 5.19, 95% CI, 3.10–8.69, $p < 0.001$; HR of OS, 4.27, 95% CI, 2.78–6.54, $p < 0.001$) were independent risk factors for an inferior RFS and OS (Table 2).

3.4. Association between the cribriform component and STAS

Univariate logistic regression analyses showed that pathological tumor stage (pT) ($p = 0.003$), pathological lymph node stage (pN) ($p < 0.001$), the solid component ($p = 0.047$), the micropapillary component ($p = 0.049$), and the cribriform component ($p < 0.001$) were potential predictive factors for the presence of STAS (Table 3). After this, we tested these variables in a multivariate analysis, which further identified that the cribriform component (odds ratio [OR], 2.21, 95% CI, 1.02–4.77, $p = 0.044$) was an independent risk factor for the presence of STAS (Table 3).

3.5. STAS affected survival in adenocarcinoma with a cribriform component

Among patients with a cribriform component, the survival analyses indicated that cribriform component present (Crib+)/spread through air spaces positive (STAS+) patients had significantly inferior outcomes when compared with Crib+/spread through air spaces negative (STAS-) patients (RFS: 5-year rate, 4% vs. 32%, $p < 0.001$; OS: 5-year rate, 2% vs. 21%, $p < 0.001$) (Fig. 3). Moreover, both Crib+/STAS + and Crib+/STAS- patients experienced inferior RFS and OS compared with those in the absence of a cribriform component (RFS: cribriform component absent [Crib-] vs. Crib+/STAS-: 5-year rate, 71% vs. 32%, $p < 0.001$; Crib- vs. Crib+/STAS+: 5-year rate, 71% vs. 4%, $p < 0.001$; OS: Crib- vs. Crib+/STAS-: 5-year rate, 57% vs. 21%, $p < 0.001$; Crib- vs. Crib+/STAS+: 5-year rate, 57% vs. 2%, $p < 0.001$) (Fig. 3).

Multivariate Cox regression analyses further confirmed that STAS was an independent risk factor for inferior RFS (HR, 3.17, 95% CI, 1.61–6.26, $p = 0.001$) and OS (HR, 3.64, 95% CI, 1.90–6.96, $p < 0.001$) in LUAD patients with a cribriform component (Supplementary Table).

4. Discussion

The presence of a cribriform component was associated with poor survival in patients with LUADs, as has been reported previously [10–14]. In addition, STAS, as a new recently proposed concept, has been found to be a significant predictor of inferior survival rates for LUAD patients [19–22,24–27]. Studies have shown that the two histological features were associated with some similar clinicopathological factors, such as higher tumor stage [10,17], smoking [14,22], and especially the presence of a solid-predominant subtype [12,19,25]. To date, there has been no study assessing the relationship between the cribriform component and STAS in pathological stage I-III LUAD. Therefore, we investigated the underlying association between the cribriform component and STAS, and focused further on their joint influence on patient prognosis. The design idea of this study has been shown in the Graphical Abstract. Ultimately this will enable us to find

Table 2
Cox Proportional-Hazards Regression Model for Recurrence-free Survival and Overall Survival in Patients with Stage I-III Adenocarcinoma.

Variables	Recurrence-free Survival			Overall Survival		
	Univariate Analysis	Multivariate Analysis		Univariate Analysis	Multivariate Analysis	
	p	HR(95%CI)	*p*	*p*	HR(95%CI)	*p*
Sex (male vs. female)	0.091			0.243		
Age (> 65 vs. ≤ 65)	0.641			0.967		
Smoking (Yes vs. No)	0.030	0.942(0.605-1.467)	0.790	0.192		
pT	< 0.001		< 0.001	< 0.001		< 0.001
T1		0.014(0.004-0.047)	< 0.001		0.020(0.005-0.046)	< 0.001
T2		0.057(0.018-0.177)	< 0.001		0.168(0.074-0.353)	< 0.001
T3		0.148(0.047-0.485)	0.001		0.517(0.304-0.870)	0.012
T4		1			1	
pN	< 0.001		< 0.001	< 0.001		< 0.001
N0		0.013(0.005-0.033)	< 0.001		0.053(0.022-0.129)	< 0.001
N1		0.214(0.122-0.378)	< 0.001		0.110(0.050-0.242)	< 0.001
N2		1			1	
LC (present vs. absent)	< 0.001	0.372(0.164-0.843)	0.018	< 0.001	0.478(0.261-0.873)	0.016
AC (present vs. absent)	0.001	0.891(0.539-1.472)	0.652	0.078		
SC (present vs. absent)	< 0.001	0.793(0.479-1.312)	0.367	< 0.001	0.819(0.526-1.274)	0.376
PC (present vs. absent)	0.885			0.758		
MC (present vs. absent)	< 0.001	1.259(0.760-2.088)	0.371	< 0.001	1.227(0.781-1.927)	0.375
CC (present vs. absent)	< 0.001	2.820(1.679-4.735)	< 0.001	< 0.001	2.729(1.737-4.288)	< 0.001
STAS (positive vs. negative)	< 0.001	5.185(3.095-8.687)	< 0.001	< 0.001	4.266(2.782-6.542)	< 0.001

HR, hazard ratio; *CI*, confidence interval; *pT*, pathological tumor stage; *pN*, pathological lymph node stage; *LC*, lepidic component; *AC*, acinar component; *SC*, solid component; *PC*, papillary component; *MC*, micropapillary component; *CC*, cribriform component; *STAS*, spread through air spaces.
Smoking: current smoker or former smoker (yes) and never smoker (no).
Variables with *p*-value < 0.05 in univariate models were analyzed in multivariate analysis model.

Table 3
Logistic Regression Model for STAS-positive Status Patients with Stage I-III Adenocarcinoma.

Variables	Univariate Analysis	Multivariate Analysis	
	p	OR(95%CI)	*p*
Sex (male vs. female)	0.217		
Age (> 65 vs. ≤ 65)	0.727		
Smoking (Yes vs. No)	0.851		
pT	0.003		0.037
T1		0.346(0.031-0.701)	0.039
T2		0.534(0.042-0.755)	0.042
T3		0.783(0.070-0.916)	0.028
T4		1	
pN	< 0.001		0.048
N0		0.259(0.079-0.849)	0.049
N1		0.392(0.134-0.946)	0.046
N2		1	
LC (present vs. absent)	0.135		
AC (present vs. absent)	0.507		
SC (present vs. absent)	0.047	0.744(0.360-1.540)	0.426
PC (present vs. absent)	0.167		
MC (present vs. absent)	0.049	0.755(0.317-1.800)	0.526
CC (present vs. absent)	< 0.001	2.207(1.022-4.767)	0.044

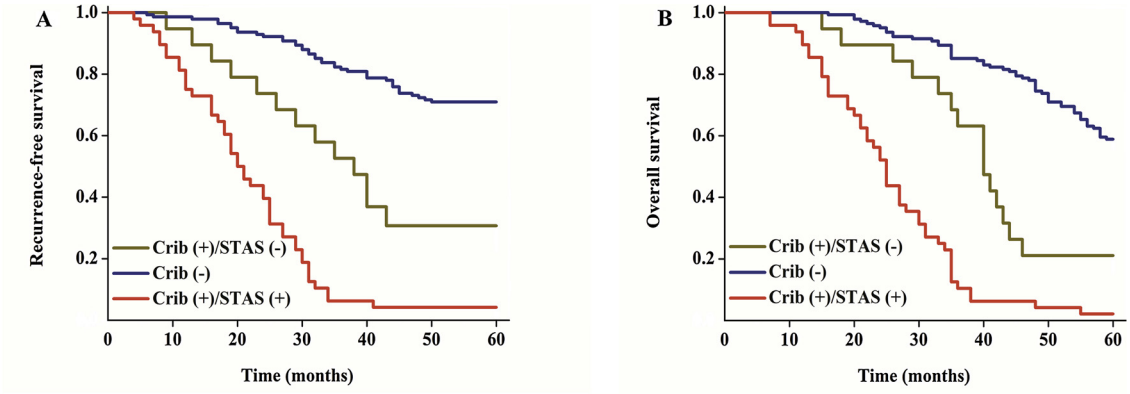
OR, odds ratio; *CI*, confidence interval; *pT*, pathological tumor stage; *pN*, pathological lymph node stage; *LC*, lepidic component; *AC*, acinar component; *SC*, solid component; *PC*, papillary component; *MC*, micropapillary component; *CC*, cribriform component; *STAS*, spread through air spaces.
Smoking: current smoker or former smoker (yes) and never smoker (no).
Variables with *p*-value < 0.05 in univariate models were analyzed in multivariate analysis model.

potential pathological mechanisms for the poor outcomes in patients presenting with a cribriform component in LUADs.

Previous studies of various carcinomas including prostate cancer [28] and colonic adenocarcinoma [29] have found that the cribriform component represents an adverse prognostic factor. Therefore, the cribriform component is not only a novel morphological finding but also a risk factor for an inferior prognosis. As observed by Kuang et al. [12], the cribriform component was associated with EGFR mutation ($p = 0.016$), AKT1 mutation ($p = 0.038$), and ALK rearrangement ($p < 0.001$). Another study characterized that the highest rate of somatic KRAS mutation was found in the cribriform component among all components [11]. In addition, the cribriform component appeared frequently in elderly patients along with the expression of TTF-1 and CK7 [30]. However, the clinicopathologcal characteristics of LUAD with a cribriform component has not been well characterized.

Because nearly 80% of LUADs contain two or more components in a single tumor [4,9], semi-quantitative pattern analysis was an effective predictor of patient prognosis, regardless of whether the growth pattern was an independent subtype. With a rate of 32.2% for the cribriform component (≥5%) found in all cases, our results are in agreement with the data from a previous study by Warth et al. [11] who observed that the cribriform-predominant adenocarcinoma accounted for 4.2% among all of the subtypes, and the cribriform-minor accounted for 28.6%. Meanwhile, our findings are also in coincidence with the results presented by Qu et al. [14] who reported that the cribriform component was found in 33% of the 395 LUADs. In addition, it was in line with previous studies demonstrating that the highest frequency of a cribriform component was observed in LUADs with a solid pattern (46 of 76; 60.5%) [10,12]. Our statistical data indicated that patients with a cribriform component had significantly inferior RFS (5-year rate: 12% vs. 71%, $p < 0.001$) and OS (5-year rate: 8% vs. 56%, $p < 0.001$) compared with those with no cribriform component. Besides, our analyses revealed that patients with a cribriform component had a significantly increased risk of developing both locoregional recurrences (5-year CIR, 57% vs. 20%, $p < 0.001$) and distant recurrences (5-year CIR, 31% vs. 9%, $p < 0.001$) when compared with those with no cribriform pattern. These results suggested that the cribriform component (≥5%) may be used to stratify patients with LUAD into more detailed prognostic groups.

In multivariate analysis, both the cribriform component (HR of RFS, 2.82, 95% CI, 1.68–4.74, $p < 0.001$; HR of OS, 2.73, 95% CI, 1.74–4.29, $p < 0.001$) and STAS (HR of RFS, 5.19, 95% CI, 3.10–8.69, $p < 0.001$; HR of OS, 4.27, 95% CI, 2.78–6.54, $p < 0.001$) were independent risk factors of inferior RFS and OS. Although some researchers once considered that the poor prognostic association with STAS is due to other clinicopathological factors, our study found that



Number at risk

Crib(-)	141	139	124	124	111	100	100
Crib(+)/STAS(-)	19	18	15	12	7	6	6
Crib(+)/STAS(+)	48	41	24	9	3	2	2

	HR	95%CI	*p*
Crib(-)	0.09	0.06-0.14	< 0.001
Crib(+)/STAS(-)	0.31	0.17-0.59	< 0.001
Crib(+)/STAS(+)	1		

Number at risk

Crib(-)	141	141	138	129	117	100	80
Crib(+)/STAS(-)	19	19	17	15	9	4	4
Crib(+)/STAS(+)	48	46	32	15	3	2	1

	HR	95%CI	*p*
Crib(-)	0.10	0.06-0.15	< 0.001
Crib(+)/STAS(-)	0.31	0.17-0.56	< 0.001
Crib(+)/STAS(+)	1		

Fig. 3. Recurrence-free survival (A) and overall survival (B) in patients with stage I-III lung adenocarcinoma with a cribriform component stratified by spread through air spaces (STAS). *Crib* (+): cribriform component present, *Crib* (-): cribriform component absent; *STAS* (+): spread through air spaces positive; *STAS* (-): spread through air spaces negative. *HR*, hazard ratio; *CI*, confidence interval.

STAS remained an independent prognostic predictor for worse outcomes, which was consistent with others [17–19,22,25]. Further logistic regression analyses identified that the cribriform component (OR, 2.21, 95% CI, 1.02–4.77, $p = 0.044$) was an independent risk factor for increased frequency of STAS. In view of this, we considered that the occurrence of STAS probably affected survival in adenocarcinoma patients with a cribriform component.

Among patients with a cribriform component, the survival analyses indicated that Crib+/STAS + patients had significantly inferior outcomes when compared with Crib+ /STAS- patients (RFS: 5-year rate, 4% vs. 32%, $p < 0.001$; OS: 5-year rate, 2% vs. 21%, $p < 0.001$), demonstrating the additional prognostic value provided by STAS for patients with a cribriform component. A multivariate Cox regression analysis further confirmed that STAS was an independent risk factor of inferior RFS (HR, 3.17, 95% CI, 1.61–6.26, $p = 0.001$) and OS (HR, 3.64, 95% CI, 1.90–6.96, $p < 0.001$) in patients with a cribriform component. Taken together, we consider that the existence of a cribriform component and a STAS-positive status should be regarded as synergistic prognostic factors in LUAD. Therefore, STAS may be one of the potential mechanisms by which the cribriform component leads to poor survival in postoperative patients.

There were several limitations to our study. Firstly, as with other single institutions, selection and performance bias were inevitable due to the nature of retrospection in this study. Secondly, given the small number of stage I patients with a cribriform component and STAS who underwent limited resection, we were unable to adequately assess the prognostic significance of sublobectomy in patients with Crib +/STAS + and Crib-/STAS + . Finally, lacking postoperative patient records for radiotherapy and chemotherapy, our investigation lacked a prognostic value for the adjuvant treatment.

Conclusions

Our study indicated that STAS was more frequently observed in LUAD patients with a cribriform component. Moreover, STAS could provide helpful prognostic information in patients with stage I-III adenocarcinoma with a cribriform component. Further studies are warranted to assess the prognostic impact of surgical procedures on LUADs with a cribriform component and STAS.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.06.027.

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