Ann Surg Oncol (2019) 26:1901–1908
https://doi.org/10.1245/s10434-019-07296-w

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Prognostic Impact of Tumor Spread Through Air Spaces in Sublobar Resection for 1A Lung Adenocarcinoma Patients

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ABSTRACT

Background. This study aimed to clarify differences in the prognostic impact of tumor spread through air spaces (STAS) in lobectomy versus sublobar resection (SR). The study also investigated the frequency and significance of STAS in residual lung segments.

Methods. This study identified 752 patients with p-stage 1A non-small cell lung cancer (NSCLC) from 2010 to 2012. Recurrence-free survival (RFS) and overall survival (OS) were compared. For proactive simulation of SR, 100 consecutive lobectomy specimens of p-stage 1A NSCLC were selected.

Results. The study found STAS in 182 (28.7%) of 634 lobectomy cases and 43 (36.4%) of 118 SR cases. Multivariable analysis showed that STAS was not a prognostic factor in the lobectomy group, but showed a significantly worse prognostic effect for the SR group (RFS, $P < 0.001$; OS, $P < 0.001$). In 9 of 100 simulated cases, STAS occurred in residual lung segments. The patients with T1c category disease had a significantly increased risk for the development of STAS in residual lung segments ($P = 0.033$).

Conclusions. For patients with p-stage 1A lung cancer who have undergone SR, STAS is a prognostic indicator of poor outcomes. The presence of STAS does occasionally exist in the residual lung segments.

Lobectomy has been the standard surgical procedure for clinical stage 1A non-small cell lung cancer (NSCLC) according to the latest National Comprehensive Cancer Network (NCCN) guidelines.[1] However, sublobar resection (SR), including segmentectomy and wedge resection, is considered acceptable for lower risk patients in early stages of disease.[2] Additionally, recent advances in low-dose, thin-section computed tomography (CT) have led to increased detection of small lung nodules.[3] Therefore, under certain circumstances, adoption of intentional limited resection for low-recurrence-risk patients in addition to compromised limited resection has recently increased.[4]

For SR, the tumor margin distance is considered an important issue for prevention of local recurrence.[5] In previous reports, the optional tumor margin distance is reported to be more than 2 cm, or at least the size of the nodule.[6] Some reports also have suggested that cytologically negative results of surgical margin examination in limited surgery for lung cancer showed less risk for local recurrence.[7] Additionally, many recent reports have shown that certain pathologic factors such as tumor-node-metastasis (TNM) stage,[8] tumor differentiation,[9] lymphovascular invasion,[10] and lepidic growth pattern are associated with survival and recurrence outcomes for these patients.[11] Additionally, the latest World Health Organization (WHO) classification shows the presence of tumor spread through air spaces (STAS) to be a novel factor of poor prognosis.[11,12]

Yijiu Ren, Huikang Xie and Chenyang Dai are equally contributed to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07296-w) contains supplementary material, which is available to authorized users.

First Received: 10 September 2018;
Published Online: 18 March 2019

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In lung adenocarcinoma, Kadota et al.[13] first reported the pathologic phenomenon of tumor STAS, defined as lung tumor cells spreading through the air spaces into the lung parenchyma adjacent to the tumor. Furthermore, STAS was shown to be a significant risk factor for tumor recurrence[14,15] and lymph node metastasis[16] in early-stage lung adenocarcinoma patients who underwent SR. However, the relationship between STAS and resection types as well as their effect on postoperative prognosis has not been clarified to date. Furthermore, the pathologic detection of STAS in the SR margin also is unknown.

Therefore, the current study aimed to clarify the differences in the prognostic impact of tumor spread through air spaces (STAS) between lobectomy and SR. We also investigated the frequency and significance of STAS in simulated SR.

MATERIALS AND METHODS

Patient Selection

This study was approved by the Institutional Review Board (IRB) of Shanghai Pulmonary Hospital (IRB no. K17-004-2). At Shanghai Pulmonary Hospital, 3225 patients had surgery for lung cancer from January 2010 to December 2012.

For the first retrospective study cohort, we reviewed all medical records and included 752 cases with lung adenocarcinoma 3 cm in size or smaller (p-stage 1A). The exclusion criteria ruled out neoadjuvant therapy, a diagnosis of multiple primary lung cancers, and a diagnosis of in situ or minimally invasive adenocarcinoma. All the patients included in the study were staged according to the eighth edition of the TNM classification.[17]

In this study, SR included both wedge resection and segmentectomy. Our institution chose to perform limited resection, including intentional and compromised SR, based on the indications listed later.[18] The patients had to meet all the following criteria for intentional SR: tumor smaller than 3 cm with radiologically ground glass node (C/T ratio < 0.5), tumor location within the outer third of the lung parenchyma, general well status and respiratory function for lobectomy, age ranging from 20 to 79 years, and no history of malignancy. Patients who could not tolerate a lobectomy for any of the following reasons were considered for compromised SR: very poor pulmonary function (percentage of predicted forced expiratory volume in 1 s $< 70\%$), age older than 80 years, and severe systemic disease.

All the patients were observed with CT scans 2 weeks after surgery, then at 4- to 6- month intervals for the first 2 years, and thereafter once a year.[19] Local recurrence was defined as appearance of tumor within the same lobe, the mediastinal lymph nodes, or the hilum. The appearance of tumor in another lobe or elsewhere outside the hemithorax was defined as distant recurrence. We combined the locoregional recurrence with distant recurrences as the recurrence.

Both telephone follow-up information and outpatient clinic revisit records were collected as survival information. The end date of follow-up assessment was 31 March 2018.

Prospective Simulated Residual Lung Segment After SR

We continuously selected 100 lobectomy specimens before dipping them into formalin. These were diagnosed as p-stage 1A NSCLC in the intraoperative frozen sections and further confirmed by paraffin pathology in January 2018 at Shanghai Pulmonary Hospital. The exclusion criteria ruled out patients with a history of neoadjuvant therapy, a diagnosis of multiple primary lung cancers, or a diagnosis of in situ or minimally invasive adenocarcinoma.

After making a small incision in the tumor, we ventilated the resected lobe through the main bronchus, which could show intersegmental planes between healthy lung segments and those collapsed with the lesion. We resected the lobe along the intersegmental planes with a new knife. We then chose the whole simulated resected margin, the side away from the lesion, for pathologic examination (Figs. 1 and S1). Two layers of each simulated SR margin were serially resected from the cut surface of the residual lung segment. The number of slides made for each layer of simulated SR margin varied from 6 to 18 depending on the lobe volume and tumor location. The distance between the simulated SR margin and the tumor was measured with a ruler on the fresh specimen.

Histopathologic Evaluation of STAS

The hematoxylin and eosin-stained slides of the resected tumor specimens from both the retrospective (re-assessed at the time of this study) and prospective cohorts and the SR margin of the prospective cohort were evaluated microscopically by two pathologists. In previous studies, STAS in lung adenocarcinoma has been well-defined.[20,21] In terms of morphology, STAS could be classified into three patterns: (1) single cells, (2) micropapillary clusters, and (3) solid nests.

Two senior pathologists classified each STAS case into one of three predominant patterns. We also adopted the methods reported by Kadota et al.[20] to distinguish STAS from alveolar macrophages and artifacts.

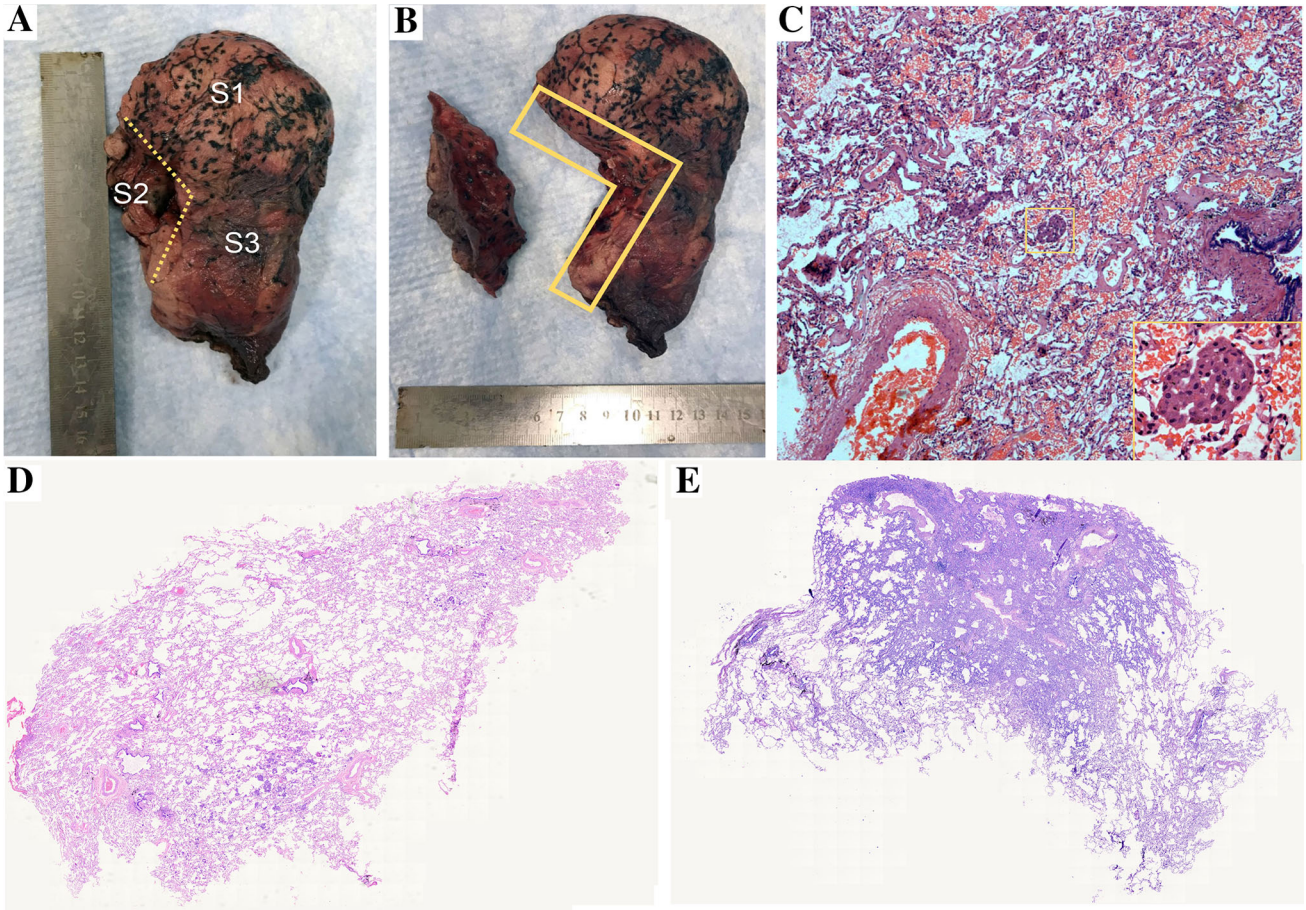

FIG. 1 Schematic diagram showing analysis of STAS in a residual lung segment after simulated sublobar resection of the right upper lobe. **a** Demarcation of the intersegmental plane by inflation of the healthy segment. The dotted line illustrates the inflation–deflation line. **b** Simulated sublobar resection margin in wireframe. **c** Morphologic features of STAS in the sublobar resection margin of the simulated residual segment (×40, ×400). **d** Morphologic features of STAS in the sublobar resection margin of the simulated residual segment (×1). **e** Typical morphologic features of malignant positive margin (×1). STAS, tumor spread through air spaces; S1, apical segment; S2, posterior segment; S3, anterior segment

Histopathologic Evaluation of Adenocarcinoma

The predominant histologic subtypes of resected specimens were assessed by two senior pathologists according to the latest lung adenocarcinoma classification. Tumors were pathologically diagnosed as predominant type such as lepidic, acinar, papillary, micropapillary, or solid. If disagreement occurred, discussion was necessary before a consensus was reached.

Statistical Analysis

All clinicopathologic and demographic data are presented as median (range) or number (%). Recurrence-free survival (RFS) and overall survival (OS) were used for survival analysis. The Kaplan–Meier method was used for survival comparison among the different groups using the log-rank test. Furthermore, a Cox proportional hazards regression model was applied to adjust for potential confounders in evaluation of RFS and OS independent risk factors. In addition, both uni- and multivariable logistic regression analyses were used to determine the association of STAS in the residual lung segments and the tumor's clinical characteristics.

In this study, a two-sided *P* value lower than 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 23 software (IBM Corporation, Armonk, NY, USA), and the survival curves were plotted using GraphPad Prism 7 software (GraphPad Software, San Diego, CA).

RESULTS

Patient Clinicopathologic Characteristics

We identified 634 and 118 patients with pathologically confirmed p-stage 1A lung adenocarcinoma in the

lobectomy and SR cohorts, respectively. Detailed clinical information is presented in Table 1. The acinar pattern was shown to be the most common predominant type in the cohort (44% in the lobectomy cohort vs 35% in the SR cohort).

Incidence and Features of STAS in p-Stage 1A Lung Adenocarcinoma in Lobectomy or SR

The study found STAS in 182 (28.7%) of 634 lobectomy cases and 43 (36.4%) of 118 SR cases. As shown in Table 1, STAS was more likely to be observed in patients with high-grade histologic adenocarcinoma (lobectomy cohort: 90% vs 10% in the lepidic subtype, 20% vs 80% in the micropapillary subtype, and 48% vs 52% in the solid subtype [$P < 0.001$]; SR cohort: 92% vs 8% in the lepidic subtype, 0% vs 100% in the micropapillary subtype, and 9% vs 91% in the solid subtype [$P < 0.001$]). The median tumor-to-STAS distance was measured under microscopy with a ruler as 1.2 mm (range 0.3–8 mm) in the lobectomy cohort and 1 mm (range 0.3–7 mm) in the SR cohort.

Tumor STAS Affects Survival in Lobectomy or SR

The survival analysis of patients with p-stage 1A lung adenocarcinoma showed that patients without STAS had a better RFS (hazard ratio [HR], 1.715; 95% confidence interval [CI], 1.109–2.652; $P = 0.008$) and OS (HR, 1.848;

TABLE 1 Characteristics of patients

Variables	Lobectomy			Sublobar resection		
	Non-STAS $n = 452$ n (%)	STAS $n = 182$ n (%)	P value	Non-STAS $n = 75$ n (%)	STAS $n = 43$ n (%)	P value
Mean age (years)	59.4 ± 8.7	59.4 ± 8.5	0.976	63.7 ± 11.4	65.9 ± 8.7	0.277
Age (years)			0.942			0.498
≤ 65	334 (74)	135 (74)		38 (51)	19 (44)	
> 65	118 (26)	47 (26)		37 (49)	24 (56)	
Gender			0.002			0.843
Male	188 (42)	100 (55)		30 (40)	18 (42)	
Female	264 (58)	82 (45)		45 (60)	25 (58)	
Smoking			0.144			0.104
Nonsmoker	357 (79)	134 (74)		62 (83)	30 (70)	
Current or ex-smoker	95 (21)	48 (26)		13 (17)	13 (30)	
CEA			0.527			0.910
Normal	439 (97)	175 (96)		73 (97)	42 (98)	
High	13 (3)	7 (4)		2 (3)	1 (2)	
Tumor location			0.169			0.262
Upper	282 (63)	105 (57)		49 (65)	27 (63)	
Middle	33 (7)	9 (5)		1 (1)	3 (7)	
Lower	137 (30)	68 (38)		25 (34)	13 (30)	
T categories			0.318			<0.001
≤ 1 cm	50 (11)	19 (10)		23 (31)	5 (12)	
1–2 cm	224 (50)	102 (56)		42 (56)	20 (46)	
2–3 cm	178 (39)	61 (34)		10 (13)	18 (42)	
Predominant subtype			< 0.001			< 0.001
Lepidic	192 (43)	20 (11)		33 (44)	3 (7)	
Acinar	177 (39)	100 (55)		28 (38)	14 (33)	
Papillary	64 (14)	33 (18)		13 (17)	15 (35)	
Micropapillary	3 (1)	12 (7)		0 (0)	1 (2)	
Solid	16 (3)	17 (9)		1 (1)	10 (23)	
Postoperative chemotherapy			0.420			0.280
No	356 (79)	138 (76)		65 (87)	34 (79)	
Yes	96 (21)	44 (24)		10 (13)	9 (21)	

STAS tumor spread through air spaces; *CEA* carcinoembryonic antigen

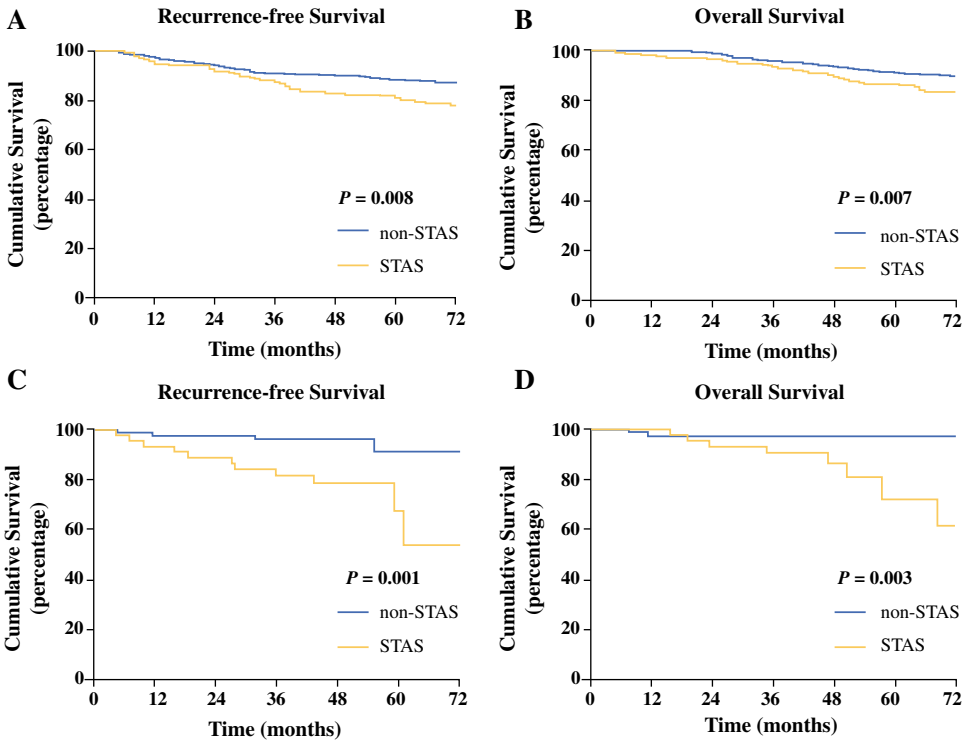

FIG. 2 **a**, **b** Recurrence-free survival and overall survival according to STAS status for patients with p-stage 1A lung adenocarcinoma who underwent lobectomy. **c**, **d** Patients who underwent sublobar resection. STAS, tumor spread through air spaces

95% CI, 1.122–3.042; $P = 0.007$) than those with STAS in the lobectomy cohort (Fig. 2a, b). Furthermore, a similar trend was also observed in the RFS analysis with the presence or absence of STATS (HR, 5.371; 95% CI, 1.843–15.65; $P = 0.001$) and in the OS analysis (HR, 7.113; 95% CI, 1.955–25.87; $P = 0.003$) of the SR cohort (Fig. 2c, d). However, in the multivariable analysis that adjusted for age, gender, smoking, carcinoembryonic antigen, tumor location, predominant subtype, and post-operative chemotherapy, STAS was not a prognostic factor for RFS (HR, 1.529; $P = 0.057$) or OS (HR, 1.638; $P = 0.052$) in the lobectomy cohort (Table 2),, whereas it remained an adverse factor for RFS (HR, 3.529; $P < 0.001$) or OS (HR, 4.547; $P < 0.001$) in the SR cohort (Table 2).

STAS Incidence and Features in the Residual Lung Segments

All cases have R0 resection in simulated SR. In residual lung segments, STAS occurred in 9 of 100 simulated cases (hematoxylin and eosin staining), of which 1 case had a microscopic single cell pattern and 8 cases had a micropapillary cluster pattern (Table 3). In this study, STAS was more likely to be observed in patients with micropapillary predominant adenocarcinoma ($P < 0.001$) and a tumor-margin distance of 1.5 cm or less ($P = 0.010$). The patients with disease in the T1c category had a significantly increased risk for the development of STAS in residual lung segments (HR, 5.868; 95% CI, 1.073–5.467; $P = 0.033$, logistic analysis).

TABLE 2 Multivariable cox proportional hazards regression model for recurrence-free survival and overall survival in patients in subgroups

Variables	Lobectomy				Sublobar resection			
	Recurrence-free survival[a]		Overall survival[a]		Recurrence-free survival[a]		Overall survival[a]	
	HR (95%CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Non-STAS	1		1		1		1	
STAS	1.529 (0.988–2.368)	0.057	1.638 (0.996–2.692)	0.052	3.529 (1.783–6.984)	< 0.001	4.547 (2.170–9.525)	< 0.001

HR hazard ratio; *CI* confidence interval; *STAS* tumor spread through air spaces

[a]Calculated from Cox regression model. The analyses adjusted for age, gender, smoking, carcinoembryonic antigen, tumor location, predominant subtype, and postoperative chemotherapy

TABLE 3 Clinical factors and pathologic status of simulated sublobar resection cases

Variables	STAS-negative $n = 91$ n (%)	STAS-positive $n = 9$ n (%)	P value
Mean age (years)	60.8 ± 9.1	65.5 ± 8.3	0.143
Age (years)			0.628
≤ 65	58 (64)	5 (56)	
> 65	33 (36)	4 (44)	
Gender			0.424
Male	48 (53)	6 (67)	
Female	43 (47)	3 (33)	
Smoking			0.796
Nonsmoker	74 (81)	7 (78)	
Current or ex-smoker	17 (19)	2 (22)	
CEA			/
Normal	91 (100)	9 (100)	
High	0 (0)	0 (0)	
Tumor location			0.533
Upper	58 (64)	5 (56)	
Middle	6 (7)	0 (0)	
Lower	27 (29)	4 (44)	
T categories			0.019
≤ 2 cm	57 (63)	2 (22)	
2–3 cm	34 (37)	7 (78)	
Predominant subtype			< 0.001
Lepidic	34 (37)	0 (0)	
Acinar	19 (21)	3 (33)	
Papillary	23 (25)	0 (0)	
Micropapillary	0 (0)	3 (33)	
Solid	7 (8)	3 (33)	
Non-adenocarcinoma	8 (9)	0 (0)	
Tumor-margin distance (cm)			0.010
≤ 1.5	51 (56)	9 (100)	
> 1.5	40 (44)	0 (0)	
Margin			
Positive	0	0	/
Negative	91 (100)	9 (100)	
Micropapillary predominant pattern			< 0.001
No	91 (100)	6 (67)	
Yes	0 (0)	3 (33)	

STAS-positive, tumor spread through air spaces remains in the residual lung segment; *CEA* carcinoembryonic antigen

DISCUSSION

Our study analyzed prognostic factors after sublobar resection for lung cancer. Interestingly, we found that the presence of STAS was strongly associated with poor outcomes of SR.

We showed that STAS is a risk factor for recurrence in SR cases. Masai et al.[14] found that STAS was a risk factor for recurrence in patients with p-T1a-bN0M0 lung adenocarcinoma who underwent SR, whereas STAS was not related to recurrence in the lobectomy cohort. They showed that the risk factors for local recurrence consisted of STAS and a margin of 1 cm or less. If the presence of STAS is detected at the surgical margin, the local recurrence rate after limited resection might be higher.

Compared with lobectomy, insufficient margin distance is reported to be an important cause of higher recurrence in SR. It is likely that SR cannot obtain enough margin distance in clinical practice. However, no solid evidence exists regarding the most appropriate surgical margin distance for limited resections. The NCCN guidelines[22] recommend a margin of 2 cm or more or at least the size of the nodules. Mohiuddin et al. found that keeping the margin distance greater than 1.5 cm can significantly decrease recurrence risk in a wedge resection cohort. However, Maurizi et al.[23] studied c-stage 1A NSCLC patients and founded the margin distance was not related to recurrence. In that study, 152 (84%) of 182 patients had a margin of 1 cm or more.

In our study, STAS was found in 9 of 100 simulated SR margins. Moreover, in the patients with a tumor-to-margin distance greater than 1.5 cm, no margin STAS was observed.

Gagné et al.[24] studied a retrospective cohort that included 1903 consecutive patients with a lung malignant neoplasm resection and found that selecting a minimum 2-cm tumor-to-margin distance for the frozen section exam would result in a 55.3% reduction of pathologic evaluations, which had a risk of 0.61% for missing a positive margin.

Considering all the aforementioned evidence combined, in SR, clinicians should try to ensure minimum surgical margins greater than 2 cm after determining the length by palpation. Nevertheless, in practice, it is better to confirm STAS status intraoperatively because of local failure associated with limited surgery.

It should be noted that several different terms exist to explain morphology similar to STAS, including "tumor islands" and "free tumor cluster."[25] These are consistently related to poor survival in a manner similar to STAS, so it can be presumed that these terms apply to a similar lung cancer pathologic phenomenon.

Furthermore, despite our results showing that STAS might be a prognostic risk factor as suggested in previous reports,[14,21] the pathologic and molecular significance of STAS remain unclear. Blaauwgeers et al.[26] reported that tumor STAS was an artifact secondary to the specimen's cut surface (STAKS). However, we found that margin STAS excludes the STAKS effect, which can be supported

by several studies. In 10 of 112 SR cases, Higashiyama et al.[27] found cytologically positive results in the surgical margin. Sawabata et al.[7] also found malignant cells in the surgical margin in 5 of 38 cases, in which 1 case had a microscopic pattern and 4 cases had an occult pattern (only cytology-positive).

As mentioned earlier, because STAS could be a confounding factor of the tumor's other biologic features, some experts still doubt use of the term STAS to describe this pathologic finding. Therefore, future studies are needed to clarify these discrepancies. Moreover, compared with vascular or pleural invasion, which can be diagnosed using immunohistochemical staining, a fast and precise way to diagnose STAS is urgently required. For that need, the molecular mechanisms of STAS urgently need to be studied.

Our study had some limitations. Limited resected cases lacked some important information, including subgroup analysis comparing wedge resection and segmentectomy, the pulmonary function results, and sufficient lymph node status. Also, the simulated SR margin could not fully represent the real SR margin. In addition, the concept of STAS in the retrospective and prospective groups via simulated SR margin may be confusing, and due to the small number of events in early-stage adenocarcinoma and combined recurrence status, the calculation power for detecting differences in the retrospective cohort might have been insufficient.

In conclusion, the presence of tumor STAS was shown to be a significant adverse indicator for lung cancer patients who have undergone SR. The presence of STAS does occasionally exist in the residual lung segments.

ACKNOWLEDGMENT This study was supported by the projects from Shanghai Hospital Development Center (SHDC12015116), the Fundamental Research Funds for the Central Universities (22120180607), the National Natural Science Foundation of China (81802256), the Shanghai Lingjun Program (2015057), and the Shanghai Pujiang Program (15PJD034).

DISCLOSURE There are no conflicts of interest.

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