Original Article

Prognostic impact of spread through air spaces in patients with ≤2 cm stage IA lung adenocarcinoma

Xiao Chen[1#], Hangcheng Zhou[2#], Mingsheng Wu[1], Meiqing Xu[1], Tian Li[1], Jun Wang[1], Xiaohui Sun[1], Yasuhiro Tsutani[3], Mingran Xie[1]

[1]Department of Thoracic Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China; [2]Department of Pathology, The First Affiliated Hospital of USTC, Division of Life Science and Medicine, University of Science and Technology of China, Hefei, China; [3]Division of Thoracic Surgery, Department of Surgery, Kindai University Faculty of Medicine, Osaka-Sayama, Japan

Contributions: (I) Conception and design: X Chen, M Xie; (II) Administrative support: H Zhou, M Xie; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: X Chen, M Wu, M Xu; (V) Data analysis and interpretation: T Li, M Wu, X Sun; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Mingran Xie, MD, PhD. Department of Thoracic Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Lujiang Road No. 17, Hefei 230001, China. Email: xmr1981@ustc.edu.cn.

Background: In 2015, the World Health Organization (WHO) included spread through air space (STAS) as a new invasive mode of lung cancer. As a new mode of lung cancer dissemination, STAS has a significant and negative impact on patient prognosis. The surgical approach as well as lymph node dissection (LND) for STAS-positive patients is currently unclear. The aim of this study was to investigate the impact of different surgical approaches to STAS and LND on the prognosis of patients with ≤2 cm stage IA lung adenocarcinoma (LUAD). This study also investigated the possible relationship between STAS and the micropapillary histological subtype and its impact on patient prognosis.

Methods: A total of 212 patients with LUAD were included in this study from January 2016 to December 2017, and the overall survival (OS) of the patients was compared. The chi-square test and *t*-test were applied to compare the clinicopathological data of the patients, and the Cox model was used for the multivariate survival analysis.

Results: Of the 212 patients, 93 (43.9%) were STAS positive. The univariate analysis showed that the surgical approach, LND type, micropapillary pattern (MP), solid pattern, and STAS were risk factors for OS. The multivariate analysis showed that the surgical approach, MP, and STAS were risk factors for OS. The STAS-positive patients who underwent lobectomy had a better prognosis than those who underwent sublobar resection; however, there was no significant difference between the two surgical procedures in the STAS-negative group. Additionally, the STAS-positive patients who underwent systematic lymph node dissection (SLND) had a better prognosis than those who underwent limited lymph node dissection (LLND); however, there was no significant difference between the two LNDs in the STAS-negative group.

Conclusions: STAS plays an important role in patient prognosis and is an independent risk factor for OS of patients with ≤2 cm stage IA LUAD. When STAS is positive, the choice of lobectomy with SLND may result in a better long-term prognosis for patients.

Keywords: Spread through air space (STAS); surgery; adenocarcinoma; prognosis

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Introduction

Presently, lung cancer is still a major threat to human health. In 2020, there were 2,206,800 new cases of lung cancer, and 1,796,700 lung cancer-related deaths, which represents the highest rate of cancer-related deaths (1). Lung adenocarcinoma (LUAD) is the most common type of non-small cell lung cancer. Currently, the main treatment for LUAD is surgery, but the long-term prognosis for even early stage LUAD patients with high-risk factors remains poor. Previous studies have identified some new high-risk factors for LUAD, including micropapillary histological subtypes, solid histological subtypes, lymphovascular invasion, and spread through air space (STAS) (2-4). The study of these high-risk factors may lead to a better long-term prognosis for patients with early stage LUAD.

In 2015 the World Health Organization (WHO) included STAS as a new invasive mode of lung cancer (5) and defined it as the "*spread of micropapillary clusters, solid nests, or single cancer cells into air spaces in the lung parenchyma beyond the edge of the main tumor*." As a new mode of lung cancer dissemination, STAS has a significant and negative impact on patient prognosis (6-9). The JCOG0802/WJOG4607L showed that segmentectomy was superior to lobectomy in terms of overall survival (OS) and the preservation of lung function in patients with peripheral early stage non-small cell lung cancer with a tumor diameter ≤2 cm (10). However, the benefits and drawbacks of sublobectomy and lobectomy in the context of high-risk conditions, such as STAS, were not addressed in this research. The close relationship between STAS and micropapillary histological subtypes has been reported (3); however, very few studies have been conducted on the effects of the mode of lymph node dissection (LND) in STAS-positive patients. This study aimed to discuss the prognostic impact of the surgical approach, as well as the LND modality in patients with ≤2 cm stage IA LUAD with the presence of STAS. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-444/rc).

Highlight box

Key findings

- For spread through air space (STAS)-positive individuals, lobectomy with systematic lymph node dissection (SLND) can result in a better long-term prognosis.

What is known and what is new?

- STAS is an independent risk factor for the prognosis of patients with lung adenocarcinoma.
- For STAS-positive patients, lobectomy with SLND might result in a better long-term prognosis.

What is the implication, and what should change now?

- Lobectomy and SLND should be an option in STAS-positive patients.

Methods

Patient selection

This study retrospectively analyzed the data of 1,316 patients with LUAD who underwent surgery at the Department of Thoracic Surgery at The First Affiliated Hospital of the University of Science and Technology of China from January 2016 to December 2017. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) have primary LUAD confirmed by postoperative pathology; (II) have a total tumor size ≤2 cm; (III) have a postoperative pathological stage of pT1a–bN0M0; and (IV) have undergone R0 resection. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had received neoadjuvant therapy; (II) had multiple nodules; and/or (III) incomplete medical records. Based on the above criteria, a total of 212 patients with LUAD were included in this study.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Affiliated Hospital of the University of Science and Technology of China (No. 2022-RE-178). The requirement of informed consent was waived for this retrospective study.

Surgery and LND modality

The main surgical procedures were lobectomy and sublobectomy. Sublobectomy included segmental lung resection and wedge lung resection. Patients underwent sublobectomy if they met the following indicators: (I) had peripheral lesions located in the outer 1/3 of the lung parenchyma and ≤2 cm in diameter or predominantly ground glass nodules; (II) had poor pulmonary function, combined cardiopulmonary disease, or who are too old to tolerate lobectomy.

Under the National Comprehensive Cancer Network guidelines, the LND modalities include systematic lymph node dissection (SLND) and limited lymph node dissection (LLND). SLND includes six groups of lymph nodes with a total of 12 lymph nodes, of which three groups are the ipsilateral intrapulmonary and hilar lymph nodes, and three groups are the ipsilateral mediastinal lymph nodes (11). SLND is routinely conducted to explore and dissect the right 2R, 3A, 3P, 4R, 7–10 groups of lymph nodes, and intrapulmonary lymph nodes, as well as the left 4L, 5–10 groups of lymph nodes, pulmonary hilar and mediastinal lymph nodes. LLND, including local LND, lymph node sampling, and no LND, is often performed in patients who do not meet the criteria for SLND. LLND is performed based on tumor size, intraoperative pathology, and the patient's overall physical condition.

Histological evaluation

Pathological staging was based on the International Association for the Study of Lung Cancer (IASLC) TNM staging system (8th edition). All patients' pathology sections were blind reviewed and reclassified by two senior clinical pathologists and re-examined by another pathologist if a discrepancy in diagnosis arose. LUAD was classified according to the pathological subtypes, including the lepidic pattern, acinar pattern, papillary pattern, micropapillary pattern (MP), and solid pattern, and recorded in 5% increments, and a subtype was considered present when a tissue component exceeded 5%.

Definition of STAS

Each diagnosis of STAS was also re-examined and reclassified by two senior clinical pathologists and re-examined by another pathologist if a discrepancy in diagnosis arose. In 2015, the WHO defined STAS as the "spread of micropapillary clusters, solid nests, or single cancer cells into air spaces in the lung parenchyma beyond the edge of the main tumor" (5). In terms of the distance of the STAS tumor cells from the main tumor, STAS was considered present even when it was present in the first alveolar layer at the tumor margin (3).

Postoperative follow-up

The follow-up was performed in two ways: regular outpatient follow-up; and telephone follow-up. Follow-up was performed every 4 months for 1–2 years, and every 6 months for 3–5 years to obtain clinical information about the patients and their OS rates. OS was defined as the time point from the start of surgery to a patient's death from any cause. The follow-up endpoint was December 2022.

Statistical analysis

Clinicopathological data of all patients were analysed by SPSS 26.0 and categorical variables were compared using chi-square test and continuous variables were compared by Student's *t*-test. The rate of survival was determined using the Kaplan-Meier method, and the log-rank test was used to analyze the differences in the survival rates across the groups. A multivariable survival analysis was carried out using the Cox model. A P value <0.05 was considered statistically significant.

Results

Patient characteristics

In total, 212 LUAD patients with a tumor size ≤2 cm were included in this study, of whom 93 were STAS positive and 119 were STAS negative. STAS was more common in visceral pleural invasion (VPI) (P=0.03), MP (P<0.001), and solid pattern (P=0.001) and less common in the papillary pattern (P=0.001); the lepidic pattern was more common in the STAS-negative patients than the STAS-positive patients (P<0.001). There were no statistically significant differences (P>0.05) in terms of gender, age, smoking history, surgery, LND modality, tumor size, preoperative co-morbidities, lymphatic invasion, and acinar pattern (*Table 1*).

Univariable and multivariable analyses of patient prognosis

A univariable survival analysis of the patients' clinical case data was conducted using the Kaplan-Meier method and the log-rank test. The results revealed that surgery type (P=0.001), LND type (P=0.04), MP (P<0.001), solid pattern (P=0.007), and STAS (P<0.001) were significantly associated with patient survival (*Table 2*). The factors that were found to be statistically significant in the univariable analysis were then included in the Cox model multivariable analysis, which showed that STAS (P=0.04), MP (P=0.02) and surgery type (P=0.03) were independent risk factors for patient prognosis (*Table 2*).

Survival rate among the patients in each group

We followed up a total of 212 patients from January 2016 to

Table 1 Baseline characteristics of the study population

Variables	STAS + (n=93)	STAS – (n=119)	χ^2	P
Sex			0.076	0.78
Male	42	56		
Female	51	63		
Age, years			0.301	0.58
≤60	52	71		
>60	41	48		
Smoking			0.042	0.84
Yes	11	13		
No	82	106		
Surgery			0.630	0.43
Lobectomy	70	95		
Sublobectomy	23	24		
Tumor size, cm			2.278	0.13
≤1	26	45		
>1, ≤2	67	74		
Preoperative comorbidities			0.644	0.42
Yes	45	51		
No	48	68		
Lymphatic invasion			1.810	0.18
Absent	75	104		
Present	18	15		
VPI			4.665	0.03
Absent	77	110		
Present	16	9		
Lymph node dissection type			0.007	0.93
LLND	71	92		
SLND	22	27		
Lepidic pattern			40.899	<0.001
Absent	56	21		
Present	37	98		
Acinar pattern			0.638	0.43
Absent	25	38		
Present	68	81		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	STAS + (n=93)	STAS – (n=119)	χ^2	P
Papillary pattern			10.226	0.001
Absent	14	41		
Present	79	78		
Micropapillary pattern			85.191	<0.001
Absent	11	90		
Present	82	29		
Solid pattern			11.117	0.001
Absent	79	116		
Present	14	3		

Preoperative complications included high blood pressure, diabetes, arrhythmia, and asthma. LLND, limited lymph node dissection; SLND, systematic lymph node dissection; STAS, spread through air space; VPI, visceral pleural invasion.

December 2022, with a total follow-up time of 84.0 months, and a median follow-up time of 67.0 months; 16 patients were lost to follow-up. The mean survival time of all patients was 76.147 months, with 1-, 3-, and 5-year survival rates of 100%, 98.6%, and 90.6%, respectively. The mean survival time of the STAS-positive patients was 68.89 months, with 1-, 3-, and 5-year survival rates of 100%, 82.7%, and 70.6%, respectively. The mean survival time of the STAS-negative patients was 81.77 months, with 1-, 3-, and 5-year survival rates of 100%, 98.3%, and 95.8%, respectively. The STAS-negative patients had a significantly better survival rate than the STAS-positive patients (*Figure 1*).

The effects of the surgical method and LND modality on patient on prognosis

We divided the patients into STAS-positive and STAS-negative groups according to the presence or absence of STAS, respectively. In the STAS-positive group, the patients who underwent lobectomy had a better prognosis than those who underwent sublobectomy (P=0.007) (*Figure 2*). In the STAS-negative group, there was no significant difference in the prognosis of patients who underwent lobectomy and those who underwent sublobectomy (P=0.27) (*Figure 3*). We also compared the differences between the LND modalities and found that in the STAS-positive group, the patients who underwent SLND had a better prognosis than those who underwent LLND (P=0.03) (*Figure 4*); however, there was no significant difference between the two LND modalities in the STAS-negative patients (P=0.67) (*Figure 5*).

Effects of STAS on the survival of patients with different proportions of micropapillary histological components

We also examined the effects of different micropapillary histological components on patient prognosis in the STAS-positive and STAS-negative groups. There was no significant difference in prognosis between the STAS-positive patients with micropapillary histological components >5% and those with micropapillary histological components ≤5% (P=0.85) (*Figure 6*); however, there was a significant difference in the prognosis of the STAS-negative patients with micropapillary histological components >5% and those with micropapillary histological components ≤5% (P<0.001) (*Figure 6*).

Discussion

A prognostic study of early stage LUAD have identified a number of high-risk factors that can have a significant impact on the long-term prognosis of patients (12). STAS was recently identified as a high-risk factor for the prognosis of lung cancer patients and has a significantly unfavorable influence on patients' long-term prognosis, and thus warrants further research (3,4,13). In our study, we found that STAS-positive patients might benefit more from undergoing lobectomy with SLND; however, in the STAS-negative patients, the performance of sublobectomy with LLND did not affect patients' long-

Table 2 The prognostic factors associated with the overall survival of patients in groups A and B by univariable analysis and multivariable Cox regression

Variables	Case	Univariate analysis		Multivariate analysis	
		Mean survival time (months)	P value	OR (95% CI)	P value
Sex			0.56		
Male	98	76.493			
Female	114	75.599			
Age, years			0.27		
≤60	123	77.339			
>60	89	74.190			
Smoking			0.99		
Yes	24	75.075			
No	188	76.124			
Surgery			0.001		0.03
Lobectomy	165	67.253		0.243 (0.069–0.864)	
Sublobectomy	47	77.933			
Tumor size, cm			0.44		
≤1	71	76.554			
>1, ≤2	141	74.923			
Preoperative comorbidities			0.10		
Yes	96	74.237			
No	116	77.496			
Lymphatic invasion			0.39		
Absent	33	75.503			
Present	179	77.848			
VPI			0.48		
Absent	25	75.555			
Present	187	76.680			
LND type			0.04		0.65
LLND	47	69.395		1.349 (0.375–4.848)	
SLND	165	77.358			
Lepidic pattern			0.27		
Absent	135	77.047			
Present	77	72.628			
Acinar pattern			0.25		
Absent	63	78.229			
Present	149	75.068			

Table 2 (*continued*)

Table 2 (*continued*)

Variables	Case	Univariate analysis		Multivariate analysis	
		Mean survival time (months)	P value	OR (95% CI)	P value
Papillary pattern			0.31		
Absent	55	76.988			
Present	157	75.064			
Micropapillary pattern			<0.001		0.03
Absent	101	82.072		0.256 (0.077–0.851)	
Present	111	70.505			
Solid pattern			0.008		0.12
Absent	194	76.993		0.494 (0.204–1.193)	
Present	18	65.556			
STAS			<0.001		0.04
Absent	119	81.769		0.363 (0.139–0.948)	
Present	93	68.590			

Preoperative comorbidities included high blood pressure, diabetes, arrhythmia, chronic obstructive pulmonary disease and asthma. OR, odds ratio; CI, confidence interval; VPI, visceral pleural invasion; LND, lymph node dissection; LLND, limited lymph node dissection; SLND, systematic lymph node dissection; STAS, spread through air space.

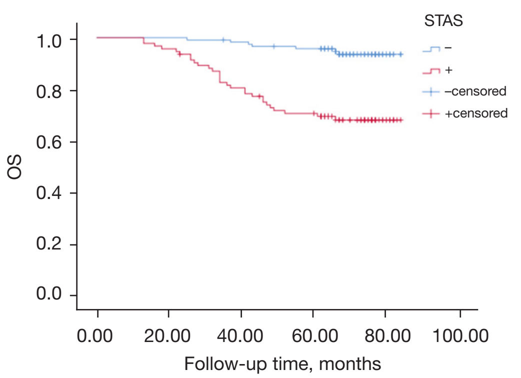

Figure 1 Overall survival according to STAS status for patients with stage IA lung adenocarcinoma (P<0.001). OS, overall survival; STAS, spread through air space.

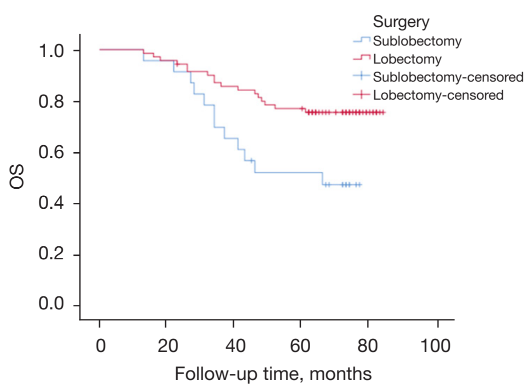

Figure 2 OS of stage IA lung adenocarcinoma patients with STAS who underwent lobectomy or sublobectomy (P=0.007). OS, overall survival; STAS, spread through air space.

term prognosis.

The present study examined 212 patients, of whom 93 were STAS positive (detection rate: 43.9%). We found that as a risk factor for LUAD, STAS significantly affected the long-term prognosis of patients, which is consistent with the results of most previous studies (8,13-16). The JCOG0802/WJOG4607L study showed that the long-term prognosis of patients undergoing segmentectomy for peripheral LUAD ≤2 cm and consolidation tumor ratio (CTR) ≤1 was significantly superior than that of patients undergoing lobectomy, and that segmentectomy preserved more lung function and improved patients' quality of life (10). However, the JCOG0802/WJOG4607L study had a number of limitations, and the findings suggested that the local recurrence rate was significantly higher in the segmentectomy group (10.5%) than the

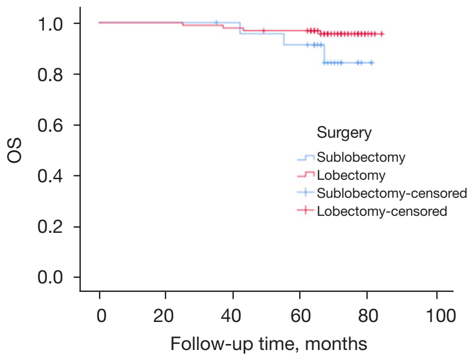

Figure 3 Overall survival of stage IA lung adenocarcinoma patients without STAS who underwent lobectomy or sublobectomy (P=0.27). OS, overall survival; STAS, spread through air space.

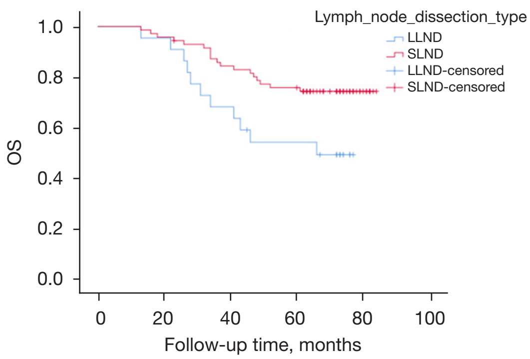

Figure 4 Overall survival of stage IA lung adenocarcinoma patients with STAS who underwent between LLND or SLND (P=0.03). LLND, limited lymph node dissection; SLND, systematic lymph node dissection; OS, overall survival; STAS, spread through air space.

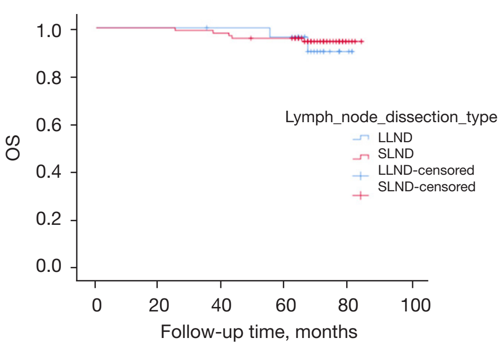

Figure 5 Overall survival of stage IA lung adenocarcinoma patients without STAS who underwent LLND or SLND in (P=0.67). LLND, limited lymph node dissection; SLND, systematic lymph node dissection; OS, overall survival; STAS, spread through air space.

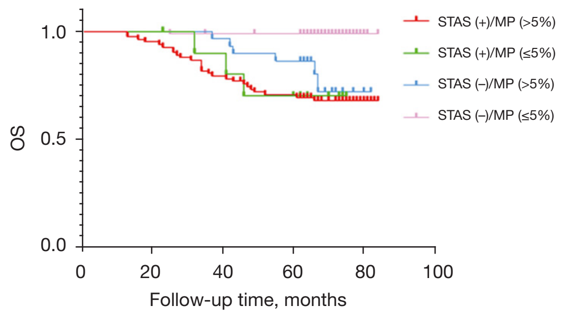

Figure 6 The OS according to STAS and MP status for patients with stage IA lung adenocarcinoma. OS, overall survival; STAS, spread through air space; MP, micropapillary pattern.

lobectomy group (5.4%), which might be due to the presence of high-risk factors, such as STAS. It is debatable whether patients with STAS should undergo sublobectomy. The results of our multifactorial survival analysis showed that the surgical modality was a risk factor for patient prognosis. Further, we found that STAS-positive patients who underwent lobectomy had a better long-term prognosis than those who underwent sublobectomy (P=0.007), but no significant difference was observed in the STAS-negative patients (P=0.27), which is consistent with the findings of Kadota (13,17).

Vaghjiani investigated the relationship between STAS and occult lymph node metastases and showed that occult lymph node metastases are more likely to occur in patients with STAS-positive LUAD and that the risk of recurrence increases as the extent of resection decreases (6). We found that the STAS-positive patients who underwent SLND had a better prognosis in than those who underwent LLND (P=0.03), but no significant difference was found in the STAS-negative patients (P=0.67). These results suggest that in STAS-positive patients, lobectomy with SLND may provide more benefit to the long-term prognosis of patients than lobectomy with LLND. Research has shown that adjuvant chemotherapy has no additional survival benefits for patients with stage IA STAS-positive LUAD, but improves the recurrence-free survival outcomes of stage IB patients with high-risk factors (18). Another study found that adjuvant chemotherapy improved the long-term prognosis of STAS-positive patients who underwent sublobectomy at stage IA, but it provided no additional survival benefits for STAS-positive patients who underwent lobectomy at stage IA (19).

In 2011, the Lung Cancer Research, International Association for the Study of Lung Cancer (IASLC), American Thoracic Society, and European Respiratory Society guidelines included the micropapillary histologic subtype as one of five subtypes of LUAD (i.e., the lepidic pattern, acinar pattern, papillary pattern, MP, and solid pattern subtypes) (20). Previous studies have shown that STAS is more prevalent in LUAD patients with the micropapillary and solid histological subtypes (8,21,22). This may be due to the lack of endothelial cell components in tumors containing the micropapillary component, which encourages the tumor cells to detach more easily from the main tumor to form STAS, and the strong invasive ability of the tumor cells in the micropapillary component, which enables the tumor cells to reattach to the alveolar wall by co-selection with alveolar vessels (22). We also observed similar results in our study; that is, the STAS-positive patients had a worse prognosis regardless of whether the micropapillary content was >5% (P=0.75), while the STAS-negative patients with a micropapillary content >5% had a worse prognosis than those with a micropapillary content ≤5% (P<0.001).

In this study, we found that the occurrence of STAS was significantly negatively correlated with lepidic (P<0.001) and papillary (P=0.001) histological subtypes. This may be related to the high detection rate of STAS in this study (43.9%). Reports of the detection rates of STAS have varied significantly in different studies (ranging from 15–55.4%) (3,23-26). These differences might stem from differences in the definition of the distance between STAS tumor cells and the main tumor in different studies. In this study, the following distance criterion was used: "*Tumor STAS was considered present when tumor STAS … was identified beyond the edge of the main tumor even if it existed only in the first alveolar layer from the tumor edge*." (3). This criterion might improve the detection rate of STAS in other histological subtypes of LUAD.

This study had some limitations. First, as a single-center retrospective study, it was difficult to completely eliminate selection bias during data collection and processing. Second, the sample size included in this study was small. Third, when comparing lobectomy *vs.* sublobar resection or SLND *vs.* LLND, patients' backgrounds were not balanced (better to use propensity score-matching). Since the presence of STAS is usually identified postoperatively, it is difficult to decide the surgical procedure based on STAS. Finally, there might have been informative bias in the diagnosis of STAS and micropapillary content during the review of pathological sections.

Conclusions

As a high-risk factor for stage IA LUAD patients, STAS plays an important role in patient prognosis. For STAS-positive patients, lobectomy with SLND might result in a better long-term prognosis. Conversely, for STAS-negative patients, sublobectomy with LLND might reduce patients' loss of lung function without affecting their long-term prognosis. However, there are still difficulties in the preoperative and intraoperative diagnosis of STAS, and further research needs to be conducted in clinical settings to determine the best surgical approach for patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-444/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-444/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-444/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-444/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The First Affiliated Hospital of the University of Science and Technology of China (No. 2022-RE-178). The requirement of informed consent was waived for this retrospective study.

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