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Tumor Spread Through Air Spaces is an Important Pattern of Invasion and Impacts the Frequency and Location of Recurrences Following Limited Resection for Small Stage I Lung Adenocarcinomas

Kyuichi Kadota, M.D., Ph.D.[1,3,5,*], **Jun-ichi Nitadori, M.D., Ph.D.**[1,6,*], **Camelia S. Sima, M.D., M.S.**[2], **Hideki Ujiie, M.D.**[1], **Nabil P. Rizk, M.D., F.A.C.S.**[1], **David R. Jones, M.D., F.A.C.S.**[1], **Prasad S. Adusumilli, M.D., F.A.C.S., F.C.C.P.**[1,4,†], and **William D. Travis, M.D.**[3,†]

[1]Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York

[2]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York

[3]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York

[4]Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, New York

[5]Department of Diagnostic Pathology, Faculty of Medicine, Kagawa University, Kagawa, Japan

[6]Department of Thoracic Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Abstract

Introduction—Tumor invasion in lung adenocarcinoma is defined as infiltration of stroma, blood vessels, or pleura. Based on observation of tumor spread through air spaces (STAS), we considered whether this could represent new patterns of invasion and investigated whether it correlated with locoregional versus distant recurrence according to limited resection versus lobectomy.

Methods—We reviewed resected small (≤2 cm) stage I lung adenocarcinomas (n=411; 1995–2006). Tumor STAS was defined as tumor cells—micropapillary structures, solid nests, or single cells—spreading within air spaces in the lung parenchyma beyond the edge of the main tumor. Competing risks methods were used to estimate risk of disease recurrence and its associations with clinicopathological risk factors.

Corresponding Authors: William D. Travis, M.D., Attending, Department of Pathology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 212-639-3325; Fax: 212-717-3576; 646-422-2016, travisw@mskcc.org, Prasad S. Adusumilli, M.D., F.A.C.S., F.C.C.P., Associate Attending, Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 212-639-8093; Fax: 646-422-2340, adusumip@mskcc.org.

*Drs. Kyuichi Kadota and Jun-ichi Nitadori contributed equally to this work.

†Drs. William D. Travis and Prasad S. Adusumilli contributed equally to this work as corresponding authors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Results—STAS was observed in 155 cases (38%). In the limited resection group (n=120), the risk of any recurrence was significantly higher in patients with STAS-positive tumors than that of patients with STAS-negative tumors (5-year cumulative incidence of recurrence [CIR], 42.6% vs. 10.9%; $P<0.001$); the presence of STAS correlated with higher risk of distant ($P=0.035$) and locoregional recurrence ($P=0.001$). However, in the lobectomy group (n=291), presence of STAS was not associated with either any ($P=0.50$) or distant recurrence ($P=0.76$). In a multivariate analysis, presence of tumor STAS remained independently associated with the risk of developing recurrence (hazard ratio, 3.08; $P=0.014$).

Conclusion—Presence of STAS is a significant risk factor of recurrence in small lung adenocarcinomas treated with limited resection. These findings support our proposal that STAS should formally be recognized as a pattern of invasion in lung adenocarcinoma.

Keywords

lung; adenocarcinoma; invasion; spread through air spaces; recurrence

INTRODUCTION

Lung adenocarcinoma invasion is traditionally defined as: 1) presence of non-lepidic patterns such as acinar, papillary, solid, or micropapillary; 2) infiltration of stroma; and 3) infiltration of blood vessels or structures such as the visceral pleura.[1] During our studies of the pathologic characteristics of lung adenocarcinoma,[2–8] we noticed tumor cells spreading in air spaces into the lung parenchyma adjacent to the edge of the tumor. We named this phenomenon “spread through air spaces” (STAS) and define it as spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor.. Literature review revealed multiple studies of various cancers in the lung that have presented with this feature reported using different terms, some of which have shown associations with poor prognosis.[9–12] Until now, this problem has received surprisingly little attention in the pathology literature, and the clinical implication of its presence in pathological specimens is not well appreciated. Therefore, using a large cohort of patients with resected small (≤2 cm) stage I lung adenocarcinoma, we investigated whether tumor STAS was a risk factor of disease recurrence according to types of surgical procedures (lobectomy or limited resection) and location of recurrence (locoregional or distant).

PATIENTS AND METHODS

Patient Cohorts

This retrospective study was approved by Memorial Sloan Kettering Cancer Center’s Institutional Review Board. Pathologic stage determination was based on the seventh edition of the *American Joint Committee on Cancer Staging Manual*.[13] We reviewed patients with lung adenocarcinomas that had been surgically resected and diagnosed as small (≤2 cm), pathological stage I disease between 1995 and 2006. Cases with neoadjuvant therapy, multiple nodules, positive surgical margin, other lung cancer surgery within the past 2 years, other disease progression, and no available tumor slides for review were excluded from the study cohort. According to these criteria, we identified a total of 411 patients. Although a

subset of these cases have been published in our previous publications,[2–8] the medical records and database were reviewed in order to update patients' follow-up as of March 2014. All recurrences were confirmed by clinical, radiological, or pathological assessment, and were classified into locoregional (local + regional) and distant recurrence.[7, 14] Local recurrence was defined as evidence of a tumor in the same lobe or at the surgical margin of the original tumor. Regional recurrence was defined as evidence of a tumor in a second ipsilateral lobe, in the ipsilateral hilar lymph nodes, or in the ipsilateral mediastinal lymph nodes. Distant recurrence was defined by evidence of a tumor in the contralateral lung, in the contralateral mediastinal, in the ipsilateral supraclavicular lymph nodes, or outside the hemithorax.

Histologic Evaluation

Tumor slides from the internal training cohort were reviewed by 2 pathologists (K.K. and W.D.T.) who were blinded to patient clinical outcomes; they used an Olympus BX51 microscope (Olympus Optical Co. Ltd., Tokyo, Japan) with a standard 22-mm diameter eyepiece.

Tumor STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor (Figure 1A and 1D) and was composed of 3 morphological patterns: 1) micropapillary structures consisting of papillary structures without central fibrovascular cores (Figure 1A and 1B),[15, 16] which occasionally form ring-like structures within air spaces (Figure 1C); 2) solid nests or tumor islands consisting of solid collections of tumor cells filling air spaces (Figure 1D and 1E)[17]; and 3) single cells consisting of scattered discohesive single cells (Figure 1F). The edge of the main tumor was defined as the smooth surface of the tumor which is easily recognizable at gross or at low-power field examination as highlighted with the dotted line in Figure 1A. Tumor STAS was considered present when tumor STAS, as defined above, was identified beyond the edge of the main tumor even if it existed only in the first alveolar layer from the tumor edge. Lesions of STAS consist of tumor cells which morphologically appear to be situated within air spaces as micropapillary clusters, solid nests or single cells that are detached from alveolar walls. This differs from lepidic growth where tumor cells grow in a linear fashion along the surface of alveolar walls. Extent of air space filling by tumor cells varied from abundant cellular infiltrates to very inconspicuous single cells or micropapillary clusters that were sometimes difficult to distinguish from alveolar macrophages. In addition, distance between tumor surface and farthest STAS from tumor edge was measured by a ruler. Since lung specimens were not consistently inflated during processing, in order to account for artifactual atelectasis, we also measured according to the number of alveolar spaces.

Tumor cells of STAS were distinguished from alveolar macrophages using the following methods. Macrophages in smokers typically have cytoplasm containing faint brown pigment and black carbon granules while in nonsmokers the pigment is lacking and cytoplasm is sometimes foamy. Nuclei are small, uniform, and regular, without atypia. Nuclear folds are frequent and nucleoli are inconspicuous or absent. In contrast, tumor cells of STAS typically lack cytoplasmic pigment or foamy cytoplasm. They often grow in cohesive clusters and nuclei are atypical with hyperchromasia and frequent nucleoli. The distinction of STAS

from artifacts was done in the following way. Tumor floaters were favored, by the presence of clusters of cells often randomly scattered over tissue and at the edges of the tissue section. Presence of jagged edges of tumor cell clusters suggested tumor fragmentation or edges of a knife cut during specimen processing rather than STAS. Linear strips of cells that were lifted off of alveolar walls also favored the presence of artifact. Identification of tumor cells distant from the main tumor was regarded as an artifact unless intraalveolar tumor cells could be demonstrated in a continuum of airspaces containing intraalveolar tumor cells back to the tumor edge.

According to the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society histological classification, the percentage of each histologic pattern—lepidic, acinar, papillary, solid, and micropapillary—was recorded in 5% increments and tumors were classified by their predominant pattern.[1] Each histologic pattern was considered present in the tumor when it comprised ≥5% of the overall tumor.[7] Presence of visceral pleural, lymphatic, and vascular invasion was also recorded.

Statistical Analysis

Associations between variables were analyzed using Fisher's exact test (for categorical variables) and the Wilcoxon test (for continuous variables). The risk of developing disease recurrence was analyzed using competing risks methods. Cumulative incidence of recurrence (CIR) of any kind (locoregional or distant) was estimated using a cumulative incidence function that accounted for death without recurrence as a competing event.[18, 19] In addition, for the analyses investigating the risk of disease recurrence according to the locations, distant or locoregional recurrence was considered as a second type of competing risk. Follow-up was calculated from date of surgery to date of disease recurrence, death from any cause, or last follow-up. Differences in CIR between groups were assessed using Gray's test (for univariate nonparametric analysis) and Fine-Gray competing risk model (for multivariate analysis) after the adjustment for important potential confounders.[19, 20] Overall survival (OS) was estimated using the Kaplan–Meier method, and nonparametric group comparisons were performed using the logrank test.

All *P*-values were based on 2-tailed statistical analysis and $P<0.05$ was considered statistically significance. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R (version 3.0.1; R Development Core Team), including the "survival" and "cmprsk" packages.

RESULTS

Patient Characteristics and Their Associations with Recurrence

Of all, 120 patients underwent limited resection (wedge resection [n=82] and sublobectomy [n=38]) and 291 underwent lobectomy. In limited resection group, 68 patients (57%) underwent lymph node dissection or sampling while, in lobectomy group, all patients underwent lymph node dissection or sampling. In the limited resection group, 28 (23%) experienced recurrence (locoregional [n=14] and distant [n=14]) and 37 (31%) died from

any cause without documented recurrence; median follow-up for patients who did not experience recurrence was 88.4 months (range, 0.2–202.6 months). In the lobectomy group, 30 (10%) experienced recurrence (locoregional [n=6], and distant [n=24]) and 62 (21%) died from any cause without documented recurrence; median follow-up for patients who did not experience recurrence was 77.5 months (range, 0.6–190.6 months). Patient characteristics and their associations with CIR, according to types of surgery, are shown in Table 1. In the limited resection group, patient age (P=0.046), tumor size (P=0.004), lymphatic invasion (P=0.001), and vascular invasion (P=0.005) were risk factors for recurrence. In the lobectomy group, patient age (P=0.022), lymphatic invasion (P=0.003), vascular invasion (P=0.005), and predominant histologic subtypes (P=0.006) were risk factors for recurrence.

Association between Clinicopathologic Factors and STAS

STAS was observed in 155 cases (38%). When classifying tumors according to predominant pattern of STAS, there were 94 tumors with micropapillary STAS, 53 with solid STAS, and 8 with single cell STAS. Associations between clinicopathologic factors and STAS are summarized in Table 1. Lymphovascular invasion and high-grade morphologic pattern in main tumors were more frequently identified in STAS-positive tumors than in STAS-negative tumors: lymphatic invasion (42% vs. 27%; P=0.002), vascular invasion (28% vs. 19%; P=0.043), micropapillary pattern (83% vs 30%; P<0.001) and solid pattern (46% vs. 30%; P=0.001). In contrast, lepidic pattern was less frequently identified in STAS-positive tumors than in STAS-negative tumors (50% vs. 69%; P<0.001).

Distance of Tumor STAS from Edge of Main Tumor

Distance between tumor surface and farthest STAS from the tumor edge was measured by a ruler with a median of 1.5 mm (range 0.2–8.5 mm) (Figure 2A). We also measured according to the number of alveolar spaces (median, 7; range, 1–58) (Figure 2B). Although we defined tumor STAS as tumor cells identified within air spaces beyond the tumor edge even if it existed only in the first alveolar layer, in 97% (n = 151) of the STAS-positive cases, tumor STAS was located beyond the first alveolar layer from the tumor edge (range, 2–58). Using an approximate alveolar size of 0.3 mm (range, 0.2–0.5 mm), we estimate a maximum distance of 1.7 cm for STAS found away from the tumor edge.

Risk of Recurrence by Tumor STAS According to Types of Surgery and Locations of Recurrence

In limited resection group, the risk of developing any types (locoregional or distant) of recurrence was significantly higher in patients with STAS-positive tumors than in patients with STAS-negative tumors (5-year CIR, 42.6% vs. 10.9%; P<0.001) (Figure 3A). In multivariate analysis, presence of tumor STAS was an independent and the only risk factor of any recurrence (hazard ratio [HR], 3.08; P=0.014) (Table 3). However, in the lobectomy group, presence of tumor STAS was not associated with an increased risk of any recurrence, compared with absence of STAS (5-year CIR, 12.7% vs. 9.5%; P=0.50) (Figure 4A).

Among patients who underwent limited resection, patients with STAS-positive tumors had a significantly increased risk of developing distant recurrences, compared to patients with STAS-negative tumors (5-year CIR, 20.4% vs. 6.8%; P=0.035) (Figure 3B). In contrast, in

the lobectomy group presence of tumor STAS was not associated with an increased risk of distant recurrence, compared with absence of STAS (5-year CIR, 9.6% vs. 7.6%; *P*=0.76) (Figure 4B).

Similarly, in the limited resection group, patients with STAS-positive tumors had a significantly increased risk of developing locoregional recurrences, compared to patients with STAS-negative tumors (5-year CIR, 22.2% vs. 4.1%; *P*=0.001) (Figure 3C).

OS by Tumor STAS According to Types of Surgery

Among patients who underwent limited resection, STAS-positive tumors was significantly associated with worse OS, compared to STAS-negative tumors (5-year OS, 59.3% [95%CI: 46.4 – 75.8] vs. 75.1% [95%CI: 65.7 – 85.8]; *P*=0.001). Among patients who underwent limited resection, although the association of OS with STAS (presence vs. absence) was statistically significant (*P*=0.045), the difference of 5-year OS rates between STAS-positive and STAS-negative patients was minimal (83.9% [95%CI: 76.9 – 91.5] vs. 88.6% [95%CI: 83.9 – 93.6]).

DISCUSSION

In this study, we have shown that STAS was a significant prognostic factor for distant and locoregional recurrence in patients undergoing limited resection. We found this in almost 40% of resected lung adenocarcinomas and observed tumor cells over 1 cm away from the edge of the tumor. This observation is the primary basis for our proposal that STAS be formally recognized as a pattern of invasion in lung adenocarcinoma. STAS is an insidious pattern of invasion because it is not visible to pathologists on gross exam and to surgeons on external examination of the tumor specimen at the time of surgery, and we are unaware of any method of radiologically detecting it.

There were several reasons why this pattern has not been previously accepted as a form of invasion. First, this pattern of invasion is unique to the lung compared with other organs because lung anatomy differs due to presence of air spaces, which normally contain air but also provide a path through which tumor cells can spread. Second, STAS is easily dismissed as an artifact where cells within air spaces were regarded as floaters or carry over due to contamination during processing. Because pathologists are not trained to look for these cells in the lung parenchyma beyond the edge of lung adenocarcinomas, STAS is mostly overlooked on microscopic review. Furthermore, due to paucity of data, there has been little emphasis on the clinical significance of this finding, and pathologists have not been compelled to look for this routinely.

Review of the literature revealed several sources of data that also support our proposal. First, studies of angiogenesis in lung cancer have classified tumors according to several different patterns of growth including alveolar patterns that correlated significantly with poor outcome.[9] In context of investigations primarily focused on lung cancer angiogenesis, it was shown that alveolar pattern of spread was non-angiogenic in contrast with other patterns of invasion which were angiogenic.[21] Second, Onozato et al studied the solid nest form of STAS (calling them “tumor islands”) with 3D reconstruction using an automated tissue

sectioning machine. They demonstrated that tumor islands were interconnected with each other and connected to solid areas in the adjacent main tumor.[22] This study was followed by a clinical study that indicated a worse prognosis for patients whose tumors had tumor islands.[17] Third, radiation therapists have been interested in "microscopic extension" in lung cancers and have emphasized the importance of clinical target volume or areas of subclinical involvement around gross tumor volume, as they design accurate radiation dose delivery.[23–26] They pointed out that these microscopic extensions spread in increasing amounts up to over 1 cm beyond the grossly visible edge of tumor, very similar to our observations.[23–26] In several articles on the topic of "microscopic extension", pathology figures illustrated typical examples of what we proposed to label STAS.[23, 24] Fourth, the adverse impact of the STAS-like pattern has not only been demonstrated in lung cancer, but also in colon cancer metastatic to the lung where patients whose metastatic tumors showed that this feature had worse prognosis compared with those that did not have this feature.[10, 11, 27] Finally, although the historical term aerogenous spread could be considered for STAS, it was used in the context of the old concept of bronchioloalveolar carcinoma, most of those cases consisted of lepidic growth, which is different from the intraalveolar localization of STAS.[12]

Identification of tumor cells within air spaces and detached from the adjacent alveolar walls in histologic sections raised important issues in the differential diagnosis. First, one can ask whether tumor cells were completely detached and floating within the air space or if they had an attachment to an alveolar wall. Onozato et al showed that "tumor islands" were interconnected with each other and with the main tumor using reconstructed 3D images of serial-sectioned slides, thereby suggesting tumor islands may have been another pattern of tumor infiltration into the lung parenchyma.[17] Whether this is true for the micropapillary or single cell patterns of STAS, particularly for tumor cells found over 1 cm away from the tumor edge is not clear. Rare cases of lung adenocarcinomas with tumor cells in air spaces within the main tumor have been reported noting a pattern resembling desquamative interstitial pneumonia (DIP).[28, 29] However, this pattern differs from STAS which is present in airspaces outside the main tumor rather than within it. The reports of a DIP pattern resemble the single cell discohesive pattern of STAS that occurred outside the main tumor, and raised the differential diagnosis of between the tumor cells of STAS and alveolar macrophages. Key points on how to distinguish STAS from artifacts and alveolar macrophages were outlined in our methods. If this distinction is difficult based on morphological criteria, immunohistochemistry for keratin and a macrophage marker such as CD68 may be helpful. The finding that STAS is an independent predictor of recurrence suggests this is clinically important and it does not represent an artifact.

In this study, we identified that the tumor STAS pattern was independently associated with high risk of recurrence in patients undergoing limited resection but not in those undergoing lobectomy. More interestingly, the STAS pattern was a significant risk factor for locoregional recurrence, suggesting these occult tumor cells, which are invisible grossly after limited resection, may result in positive surgical margins after limited resection. However, since this was a retrospective review of cases, it was very difficult to evaluate the status of tumor STAS in the surgical margins. We also had insufficient data to calculate the significance of differing amounts of STAS. We measured the distance from the tumor

surface to the farthest tumor STAS; however, our specimens were not consistently inflated making these measurements challenging. Therefore, further investigation is warranted to study the clinical impact of confirming whether surgical margins are microscopically free of the tumor STAS pattern in limited resection specimens and whether the tumor STAS pattern can be detected on frozen sections during surgery. This may help thoracic surgeons make clinical decisions on additional treatments, intraoperatively and postoperatively. In addition, further studies are required to determine whether or not the extent of tumor STAS, in terms of circumference involved or distance from the tumor edge, is associated with disease recurrence. Defining the edge of the tumor may be difficult in some cases particularly with a significant micropapillary component; however, in most cases this can be achieved. Tumor cells identified as STAS beyond the border of the tumor should not be included in the comprehensive histologic subtyping of lung adenocarcinomas as they represent a pattern of invasion. It is possible that one of the reasons why small percentages (5%) of a micropapillary pattern in lung adenocarcinomas have been reported to correlate with poor prognosis may be because these actually represented micropapillary STAS.[7, 16] This also needs to be investigated in future studies.

The most important clinical implication of finding STAS in a resection specimen is the possibility of a positive or close margin that might easily be missed by pathologists who do not specifically look for this lesion. Our data suggested that presence of STAS was particularly important in patients who had undergone limited resections for lung adenocarcinoma. Lobectomy with hilar and mediastinal lymph node dissection was the current gold standard for treatment of early-stage lung cancers, whereas multiple studies have suggested that peripheral small (≤2 cm) lung cancers could be treated by limited resection alone; this technique may be as effective as a lobectomy with the added advantage of preserving lung function.[30–32] With recent randomized trials assessing low-dose computed tomography screening for lung cancers,[33–35] it is anticipated that an increasing number of patients will be diagnosed with early-stage small lung adenocarcinomas. Despite this, there have been no established criteria for choosing limited resection over lobectomy for the treatment of lung adenocarcinomas to date.

The micropapillary pattern has been reported to be a high-grade morphologic pattern in lung adenocarcinoma and was associated with lymphovascular invasion.[15, 16, 36, 37] In our study, STAS was more frequently identified in cases that had a micropapillary pattern in the main tumor. However, for adenocarcinoma subtyping the micropapillary pattern is assessed only within the borders of the tumor edge while STAS represents a pattern of invasion within surrounding airspaces beyond the edge of the tumor. Although the STAS pattern was also positively associated with presence of lymphovascular invasion, which has been considered a significant poor prognostic factor, tumor STAS was an independent risk factor of recurrence in the limited resection group while vascular invasion was not. Our group has recently demonstrated that presence (≥5%) of micropapillary pattern identified a high-risk group for recurrence among patients who underwent limited resection but not those who underwent lobectomy,[7] thereby suggesting that patients whose tumors were pathologically diagnosed as having micropapillary pattern after limited resection may benefit from completion lobectomy.

In conclusion, we have shown that STAS pattern is a significant risk factor of disease recurrence in small (≤2 cm) stage I lung adenocarcinoma treated with limited resection. This supports our proposal that STAS be formally recognized as a pattern of invasion in lung adenocarcinoma. Although we did not study STAS in other histologic types of lung cancer, we have seen it in our clinical work and prior literature suggests that it occurs in other histologies such as squamous cell carcinoma.[25] Furthermore, based on this observation, in the future it is possible for patients who undergo limited resection that the identification of STAS may help clinicians make better clinical decisions on postoperative therapies, such as adjuvant chemotherapy and completion of lobectomy with lymph node dissection. Hopefully, our findings will encourage further investigations to determine whether the tumor STAS pattern is microscopically recognizable on frozen sections of lung adenocarcinoma, which may help thoracic surgeons choose lobectomy over limited resection for appropriate patients intraoperatively. In addition, the issues in surgical margin by tumor STAS, especially in limited resection cases, should be investigated and resolved in the prospective studies in the future. Further work is also needed at the molecular level to better understand what are the genetic and biological characteristics of tumor cells that make them prone to loss of cohesiveness and spread through air spaces.

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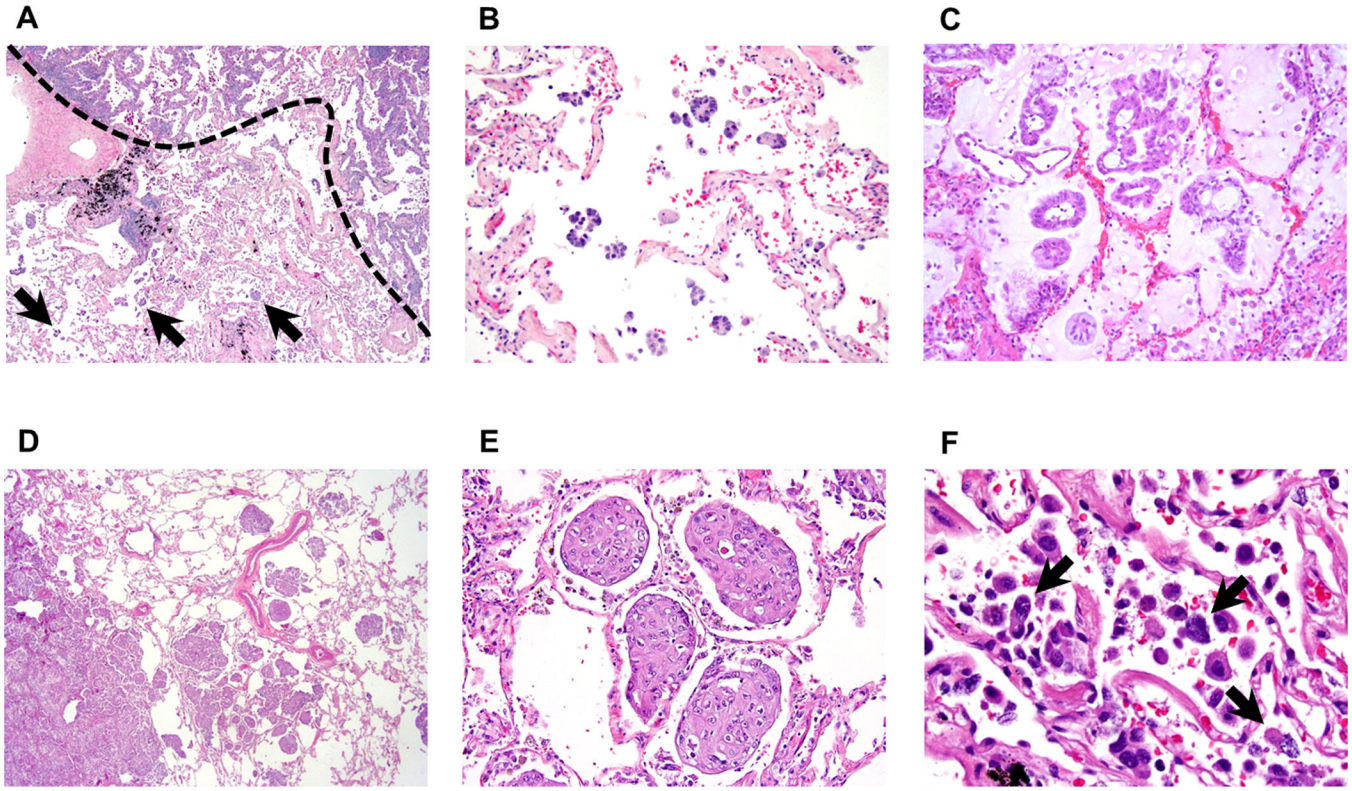

Figure 1. Morphologic features of tumor spread through air spaces (STAS) pattern (original magnification: ×20 in A and D; ×200 in B, C and E; ×400 in F)

(A) Micropapillary pattern STAS (arrows) identified within air spaces in the lung parenchyma beyond the edge (a dotted line) of the main tumor. (B) Micropapillary pattern STAS consisting of papillary structures without central fibrovascular cores. (C) Micropapillary pattern STAS forming ring-like structures within air spaces. (D) Solid pattern STAS identified within air spaces in the lung parenchyma beyond the edge of the main tumor. (E) Solid type STAS consisting of solid collections of tumor cells filling air spaces. (F) Single cell pattern STAS consisting of scattered discohesive single cells (arrows).

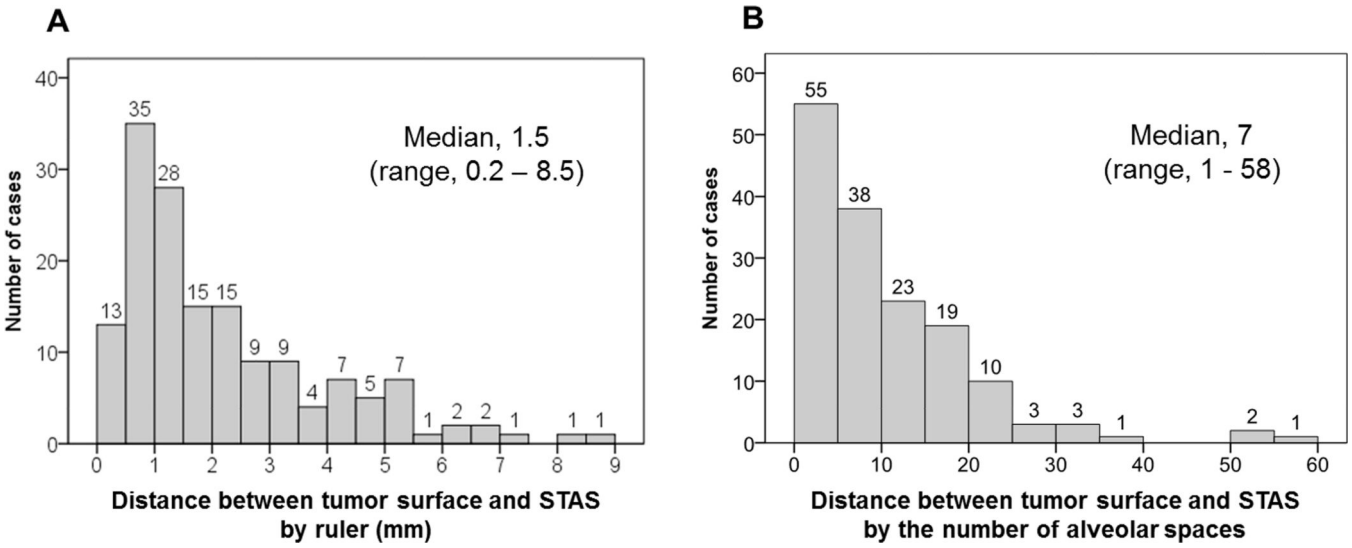

Figure 2. Distance of tumor spread through air spaces (STAS) from edge of main tumor

(A) Distance between tumor surface and farthest STAS away from the tumor edge was measured by a ruler with a median of 1.5 mm (range 0.2–8.5 mm), and (B) according to number of alveolar spaces with a median of 7 (range 1–58).

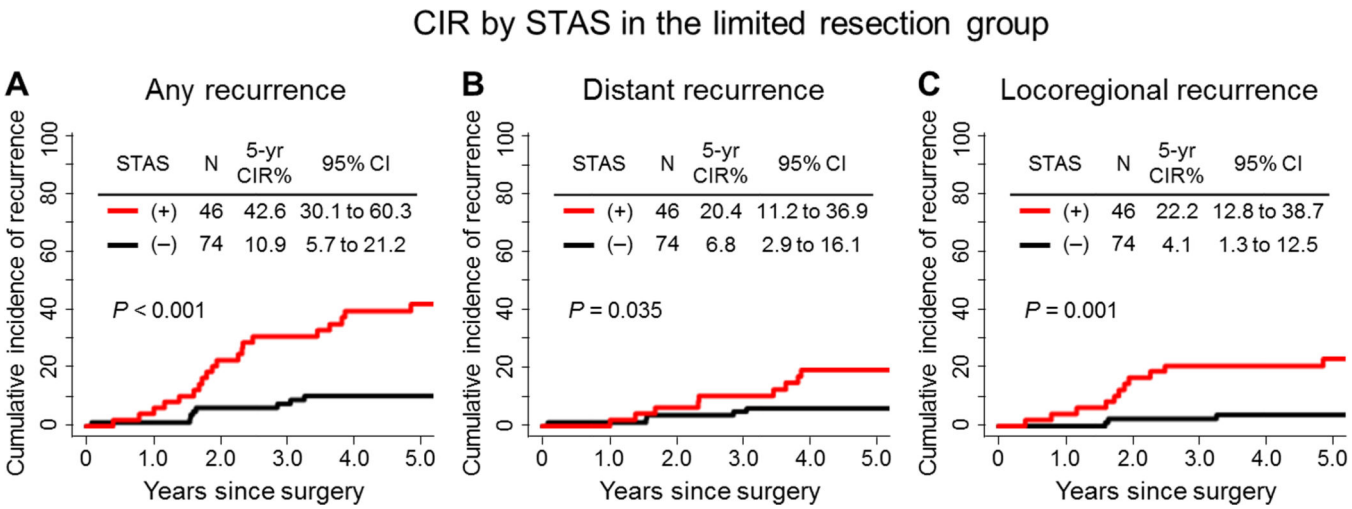

Figure 3. Cumulative incidence of recurrence (CIR) by spread through air spaces (STAS) in the limited resection group

(A) CIR for any recurrence of patients with STAS-positive tumors was significantly higher than for patients with STAS-negative tumors (5-year CIR, 42.6% vs. 10.9%; $P<0.001$). (B) CIR for distant recurrence of patients with STAS-positive tumors was significantly higher than for patients with STAS-negative tumors (5-year CIR, 20.4% vs. 6.8%; $P=0.035$). (C) CIR for locoregional recurrence of patients with STAS-positive tumors was significantly higher than for patients with STAS-negative tumors (5-year CIR, 22.2% vs. 4.1%; $P=0.001$).

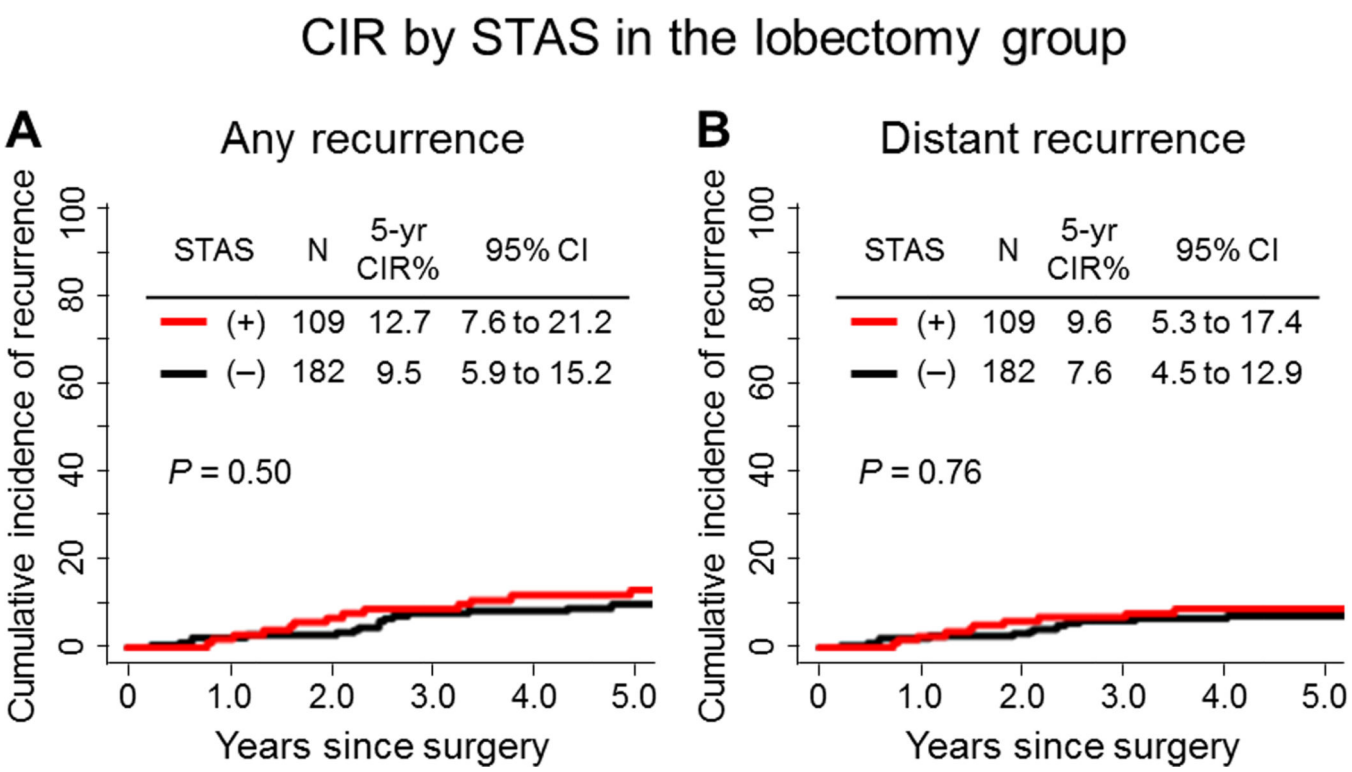

Figure 4. Cumulative incidence of recurrence (CIR) by spread through air spaces (STAS) in the lobectomy group

(A) Presence of tumor STAS was not associated with risk of any recurrence compared with absence of STAS (5-year CIR, 12.7% vs. 9.5%; *P*=0.50). (B) Presence of tumor STAS was not associated with risk of distant recurrence compared with absence of STAS (5-year CIR, 9.6% vs. 7.6%; *P*=0.76).

Table 1

Associations between Clinicopathologic Factors and Tumor STAS

Variables	All patients		STAS				*P*
			Absent		Present		
	N	%	N	%	N	%	
Age, years							0.090
Median	68		68		67		
Range	28 – 89		28 – 89		36 – 87		
Gender							0.22
Female	247	60	148	58	99	64	
Male	164	40	108	42	56	36	
Smoking							0.62
Never	52	13	34	13	18	12	
Former/current	359	87	222	87	137	88	
Surgery							0.87
Lobectomy	291	71	182	71	109	70	
Limited resection	120	29	74	29	46	30	
Tumor size, cm							0.71
Median	1.5		1.5		1.5		
Range	0.3–2.0		0.3–2.0		0.3–2.0		
Pleural invasion							0.47
Absent	364	89	229	89	135	87	
Present	47	11	27	11	20	13	
Lymphatic invasion							**0.002**
Absent	277	67	187	73	90	58	
Present	134	33	69	27	65	42	
Vascular invasion		0					**0.043**
Absent	319	78	207	81	112	72	
Present	92	22	49	19	43	28	
Lepidic pattern							**<0.001**
Absent	158	38	80	31	78	50	

Variables	All patients		STAS				*P*
			Absent		Present		
	N	%	N	%	N	%	
Present	253	62	176	69	77	50	
Acinar pattern							0.15
Absent	15	4	12	5	3	2	
Present	396	96	244	95	152	98	
Papillary pattern							**<0.001**
Absent	112	27	88	34	24	15	
Present	299	73	168	66	131	85	
Micropapillary pattern							**<0.001**
Absent	205	50	178	70	27	17	
Present	206	50	78	30	128	83	
Solid pattern							**0.001**
Absent	263	64	179	70	84	54	
Present	148	36	77	30	71	46	

STAS, spread through air spaces

Significant *P*-values are shown in bold

Table 2

Clinicopathologic Associations with Recurrence According to Types of Surgery

Variables	Limited Resection Group (n = 120)					Lobectomy Resection Group (n = 291)				
	N	%	5-yr CIR%	95% CI	*P*	N	%	5-yr CIR%	95% CI	*P*
Age, years					**0.046**					**0.022**
<65	41	34	34.2	22.2 to 52.7		127	44	15.3	10.0 to 23.5	
≥65	79	66	17.1	10.4 to 28.1		164	56	7.1	4.0 to 12.6	
Gender					0.40					0.22
Female	73	61	19.8	12.3 to 31.8		174	60	8.7	5.2 to 14.3	
Male	47	39	27.8	17.4 to 44.5		117	40	13.6	8.5 to 21.9	
Smoking					0.79					0.25
Never	15	13	20.6	7.2 to 59.1		37	13	5.7	1.4 to 22.3	
Former/Current	105	88	23.3	16.4 to 33.2		254	87	11.5	8.0 to 16.4	
Tumor size					**0.004**					0.64
≤1.0 cm	35	29	5.9	1.5 to 23.1		50	17	12.9	6.0 to 27.6	
>1.0 cm	85	71	29.9	21.4 to 41.6		241	83	10.2	6.9 to 15.1	
Pleural invasion					0.87					0.13
Absent	102	85	23.1	16.1 to 33.2		262	90	9.9	6.7 to 14.4	
Present	18	15	22.2	9.1 to 54.4		29	10	17.4	7.7 to 39.2	
Lymphatic invasion					**0.001**					**0.003**
Absent	75	63	13.7	7.6 to 24.5		202	69	7.0	4.1 to 11.8	
Present	45	38	38.6	26.5 to 56.4		89	31	19.2	12.3 to 29.9	
Vascular invasion					**0.005**					**0.005**
Absent	96	80	17.1	10.9 to 26.8		223	77	7.8	4.9 to 12.5	
Present	24	20	45.8	29.2 to 72.0		68	23	20.0	12.2 to 32.8	
Histologic subtype					0.22					**0.006**
AIS + MIA	3	3	0.0	NA		6	2	0.0	NA	
Lepidic	18	15	6.4	0.9 to 45.7		20	7	5.0	0.7 to 35.5	
Acinar	49	41	31.2	20.4 to 47.8		145	50	8.2	4.6 to 14.5	
Papillary	24	20	29.2	15.3 to 55.5		66	23	8.3	3.6 to 19.4	
Micropapillary	8	7	25.0	6.9 to 90.9		10	3	20.0	5.3 to 75.4	

Variables	Limited Resection Group (n = 120)					Lobectomy Resection Group (n = 291)				
	N	%	5-yr CIR%	95% CI	*P*	N	%	5-yr CIR%	95% CI	*P*
Solid	16	13	13.0	3.4 to 50.5		36	12	30.2	17.7 to 51.4	
Others*	2	2	NA	NA		8	3	NA	NA	

CIR, cumulative incidence of recurrence; CI, confidence interval; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; NA, not applicable

*Others include invasive mucinous and colloid predominant adenocarcinomas

Significant *P*-values are shown in bold

Table 3

Multivariate Analysis for Recurrence in the Limited Resection Group

Variables		HR	95% CI	*P*
Age, years	≥65 vs. <65	0.50	0.24 to 1.05	0.068
Tumor size, cm	>1 vs. ≤1	4.00	0.90 to 17.80	0.069
Vascular invasion	present vs. absent	2.10	0.97 to 4.56	0.061
STAS	present vs. absent	3.08	1.26 to 7.56	**0.014**

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

Significant *P*-values are shown in bold.