Review

Spread Through Air Spaces (STAS): A New Pathologic Morphology in Lung Cancer

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Abstract

In 2015, the World Health Organization classification of lung cancer proposed the concept of spread through air spaces (STAS) as a new pattern of invasion in lung adenocarcinoma. The definition of STAS included one or more pathologic micropapillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma, and separation from the main tumor other than tumor islands. The roles of STAS has been investigated in many studies. The results indicated that STAS is associated with key clinical variables and the prognosis of patients both in lung adenocarcinoma, lung squamous cell carcinoma, small-cell lung cancer, and lung pleomorphic carcinoma. This mini review will be focused on the developments and perspectives of STAS in lung cancer.

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Introduction

Since the concept of spread through air spaces (STAS) was proposed as an invasive pattern of lung adenocarcinoma (AdC) in 2015, this topic has been the focus of recent research. The roles of STAS, not only in AdC, but also in lung squamous cell carcinoma (SCC), small-cell lung cancer (SCLC), and lung pleomorphic carcinoma, are being investigated in a number of studies. Here, we will review the developments and perspectives of STAS in lung cancer.

Definition of STAS

In the past few decades, despite improvements in early detection and treatment, lung cancer remains the most common malignant tumor with the highest incidence and mortality worldwide.[1] Lung cancer invasion, such as lymphovascular or pleural invasion and infiltration of stroma, is generally associated with a poor prognosis. The presence of tumor cells in air spaces is regarded as a manifestation of the invasiveness of lung cancer. As early as 2002, the micropapillary component, which is defined as small papillary clusters of glandular cells growing within air space, was demonstrated to be probable metastasis in AdC.[2] In 2011, a new classificationof AdC by the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society/European Respiratory Society recommended the addition of micropapillary predominant AdC as a major histologic subtype owing to its association with poor prognosis.[3] In 2013, Onozato proposed the term "tumor islands," which refers to large collections of tumor cells isolated within alveolar spaces.[4] Tumor islands are also associated with higher invasion, and are different from the micropapillary pattern with a distance of at least a few alveoli from the main mass. However, 3-dimensional reconstruction showed that they are still connected to the main tumors. In 2015, the World Health Organization (WHO) classification of lung cancer proposed the concept of "spread through air spaces" as a new pattern of invasion in AdC, which includes 1 or more pathologic micropapillary clusters, solid nests or single cells beyond the edge of the tumor into air spaces in the surrounding lung parenchyma, and separation from the main tumor other than tumor islands.[5]

Although the precise definition of STAS has been proposed by WHO, further classification of STAS according to pathologic characteristics is different in recent studies. The most common grouping method of subtypes in STAS is also based on morphologic features, including single cell, small clusters, and tumor cell nests, similar to the definition by WHO. In the Warth et al study, the grade of STAS was divided into 2 groups according to the distance between the STAS and primary lesions.[6] They defined a solid cell nest no more than 3 alveoli away from the main tumor mass as limited STAS, and a tumor cell nest more than 3 alveoli away from the primary tumor was defined as extensive STAS. Another

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classification of STAS was proposed in the study by Toyokawa et al. In their study, the grade of STAS was grouped based on the quantity of spread cells or clusters, including no STAS, low STAS (1-4 cells or clusters), and high STAS (> 4 cells or clusters).[7] A similar classification of STAS was given in a semi-quantitative study.[8] In these 3 studies, the impact of STAS on clinical characteristics or prognosis of AdC correlated with the grades of STAS. This may indicate that features of STAS such as quantity, morphology, and distance could change with the progression of tumor, and invasiveness may be associated with the degree of these features, similar to the influence of tumor differentiation grade. These studies provide evidence on the grade of STAS; however, more research is needed for accurate classification.

STAS in Lung AdC

In recent years, many studies had investigated the correlation between STAS and the clinical parameters and prognosis of lung cancer. The majority of these studies focused on AdC, and a number of tumor-related factors were considered to be influenced by STAS. The incidence of STAS in AdC ranged from 14.8% to 56.4%, and STAS was demonstrated to have an association with AdC histologic type. In a study of 276 cases of stage I AdC, the presence of STAS was frequently found in invasive histologic patterns (subtypes of AdC other than atypical adenomatous hyperplasia, adenocarcinoma in situ, and minimally invasive adenocarcinoma).[7] Furthermore, a study that included 208 cases of stage I AdC showed that STAS was significantly associated with solid predominant AdC.[8] In the research by Warth et al, this large cohort study on STAS included 569 AdC cases without stage selection, and the results showed that micropapillary predominant AdC had the highest rate of STAS (91.3%), which was mainly extensive STAS as in the aforementioned definition.[6] Similar results were observed in another study based on 316 Korean AdC cases, which showed that the incidence of STAS was significantly higher in AdC with micropapillary pattern.[9] A micropapillary or solid pattern of AdC was considered to have a more aggressive malignant behavior, and these results showed that STAS may be one of the invasive mechanisms in these 2 subtypes. As a pattern of invasion, STAS is also correlated with other invasive behaviors or metastasis of AdC. By analyzing 318 cases of stage I AdC, Shiono et al proposed that STAS had a significant association with lymphovascular invasion and pleural invasion.[10] On the other hand, it is believed that STAS is related to tumor stage. Two analyses based on large populations without specific stage obtained similar results where STAS was more prevalent in high-stage AdC.[6,9] STAS is thought to have an association with a group of gene mutations in AdC. In 2 studies investigating the mutation status of epithelial growth factor receptor, STAS was confirmed to be significantly negatively associated with epithelial growth factor receptor mutation.[6,9] Warth et al evaluated the KRAS and BRAF mutation status in combination with STAS status in AdC and showed that STAS was more frequent in cases with KRAS mutation.[6] Even though STAS has only been detected in postoperative specimens so far, 2 retrospective studies examined the relationship between STAS and preoperative imaging. Shiono et al demonstrated that the positive rate of STAS was significantly higher in cases with solid nodules than in those with non-solid nodules on chest computed tomography scanning.[10] Toyokawa evaluated the primary tumor in preoperative positron emission tomography-computed tomography and concluded that STAS positivity was significantly associated with larger radiologic tumor diameter, higher consolidation/tumor ratio, and higher maximum standardized uptake value.[7] Furthermore, males and smoking history were also considered to have an association with STAS.[10]

To date, many studies have investigated the correlation between STAS and the prognosis of AdC. In a recent study that included 383 stage IA cases and 161 stage IB cases of AdC, patients with positive STAS had a significantly worse recurrence-free survival (RFS) and overall survival (OS) than those who were STAS-negative.[11] Furthermore, the authors found that patients with stage IA AdC and STAS positivity had a similar prognosis to those with stage IB AdC. However, they failed to identify this significant association in patients with a tumor size no more than 2 cm.[11] Kadota et al validated the relationship between prognosis of early stage AdC and STAS status in combination with type of surgery. In this large cohort study involving 411 cases with stage I AdC, researchers discovered that patients with positive STAS who underwent limited resection had higher risks of distant and locoregional recurrence than those with negative STAS; however, this significant risk was not found in the lobectomy group.[12] Therefore, they suggested that lobectomy or postoperative chemotherapy should be considered if STAS is identified in frozen sections from patients treated with limited resection. When histologic type was taken into consideration, one study of AdC with micropapillary pattern analyzed coexistent free tumor clusters (STAS excluded single cell), the authors found that patients who were free tumor cluster-positive experienced significantly worse 5-year RFS and higher locoregional recurrence.[13] Another study analyzed all subtypes of growth patterns, and the impact of STAS on survival was particularly evident in papillary predominant and micropapillary predominant AdC, rather than lepidic, acinar, solid predominant, or cribriform AdC.[6] Other studies also demonstrated reduction in OS or RFS in patients who were STAS-positive, and multivariate analysis showed that STAS positivity was a significant predictor of survival or recurrence.[7-10] However, in the large cohort study by Warth et al, it was found that STAS positivity was not a risk factor for OS or disease-free survival when both stage and STAS status were included in the multivariate analysis.[6,14] These results may indicate that STAS has an influence on the prognosis of AdC; however, further research is needed to confirm the accurate relationship between STAS status and tumor stage.

STAS in Lung SCC

Although the concept of STAS was first validated in studies of AdC, current research has also proved that STAS plays an important role in the invasion of SCC. In a study that included 216 cases of SCC at various stages, STAS was observed in 40% of patients.[15] The evaluation of surgical specimens revealed that STAS had a significant association with lymphatic invasion and lymph node metastasis. Tumor budding, defined as a tumor nest composed of less than 5 cells present at the outer edge of the tumor, has also been demonstrated to be associated with poor prognosis in SCC, and was correlated with STAS in the study.[16] In the study by Lu et al, which included 445 stage I to III SCC cases, 30% of cases were STAS-

positive. Further analyses showed that STAS was significantly more frequent in cases with larger tumor or nuclear diameter, lymphovascular invasion, higher T or N classification, presence of necrosis, and high Ki-67 labeling index.[17] Both of these studies suggested that the positive rate of STAS increased with pathologic stage. On the other hand, STAS was also demonstrated to play a negative role in the prognosis of SCC. In the study by Kadota, STAS was significantly associated with a higher risk of locoregional or distant recurrence, and patients with positive STAS had significantly lower RFS than those without STAS. However, this statistical significance was only found in patients who underwent lobectomy, rather than patients who underwent limited resection.[15] The cumulative incidence of recurrence (CIR) and lung cancer-specific death (CID) were also used to evaluate the prognosis of SCC, and significantly higher CIR and CID values were detected in patients with STAS in stage II or stage III.[17] However, Yanagawa's research that included 220 patients with SCC showed an opposite conclusion. Forty-two cases with STAS were identified in the study, and lymphovascular invasion was associated with STAS. They documented that the presence of STAS was associated with significant worse RFS and 5-year OS only in stage I SCC, but not in stage II or stage III SCC.[18] In another study involving 44 cases of SCC, STAS-positive cases did not show a significantly worse RFS or OS compared with STAS-negative cases, possibly owing to the small number of cases.[14] In 2 studies with large populations, STAS positivity was identified as an independent risk factor for RFS or CID by multivariate analysis.[15,17]

STAS in Other Histologic Types of Lung Cancer

Compared with AdC and SCC, fewer studies have focused on SCLC. The only existing study, which was performed by Toyokawa et al, included 30 cases of resected SCLC.[19] The presence of STAS was detected in 83% of cases, and > 80% of positive STAS cases were identified as having high STAS as defined earlier. However, there was no statistically significant relationship between any of the clinical factors and STAS positivity, and no statistical significance was observed between the STAS-positive group and the STAS-negative group in terms of RFS or OS.[19] According to this study, the positive rate of STAS in SCLC was higher than that in any study of lung AdC or SCC, which indicated that STAS may play a more important role in the development of SCLC than non-SCLC. However, 83% of cases were male, and T1 stage accounted for 40% of cases in this study. The shortage of available cases and limitations of the distribution of pathologic factors may have caused the failure to detect a clinical significance. Further study based on a larger cohort population is warranted to determine the clinical significance of STAS in SCLC.

In a recent study, Yokoyama et al observed 14 (40%) cases with STAS from 35 patients diagnosed as lung pleomorphic carcinoma who underwent surgical resection.[20] Statistical analysis showed that tumor necrosis is more frequent when STAS is present, and patients with STAS had significantly worse RFS and OS. The study pointed out that STAS is a poor predictor of postoperative survival in this rare lung cancer.[20] The lung pleomorphic carcinoma has not been sufficiently characterized owing to its rarity. This report provides valuable information on the stratification and management of patients with this rare type of tumor. Moreover, Yokoyama et al validated the associations of STAS with clinicopathologic features and prognosis, which was consistent with findings in lung AdC and lung SCC. The novel findings increased the reliability of significance and prognostic implications of STAS in lung cancer. Current studies that are focusing on STAS in lung cancer are shown in Table 1.

Challenges and Perspectives

There are several controversial questions related to the role of STAS in lung cancer. First, some confounding factors may influence the judgement of STAS existence during surgical or pathologic resection, such as "spread through a knife surface (STAKS)," which means loose tissue fragments attributed to lung specimen sectioning.[21] Blaauwgeers and colleagues evaluated tumor clusters in tissue blocks cut using a clean knife used for the first time and those cut using a knife that had been used previously, and discovered that the presence of loose tissue fragments in air spaces was more frequent in the latter blocks.[21] However, Kadota et al[12] and Warth et al[6] demonstrated that STAS is not an artifact and provided the criteria for distinguishing artifacts from true STAS. Tumor floaters often presented at the edges of the tissue section or randomly scattered over tissue. The presence of jagged edges or linear strips indicated tumor fragmentation or STAKS rather than STAS. Identification of tumor cells distant from the main tumor also suggested STAKS unless intraalveolar tumor cells could be demonstrated in a continuum of airspaces containing intraalveolar tumor cells back to the tumor edge.[12] STAS were favored by the presence of tumor cells arranged in loose small groups, for which the distribution was consistent with the overall configuration of the circumferential tumor edge.[6] Lu et al evaluated 2 patients who underwent lobectomy where the main tumor was not cut by the surgeon or pathologists, and it was found that extensive STAS existed on a separate wedge specimen.[22] The other study revealed that STAS can be detected in frozen sections, and an adequate margin of frozen section was helpful for identification of STAS intraoperatively.[23] As the definition from WHO was given for STAS in 2015, although STAS does not connect with primary tumor, it does not mean that STAS have no attachment to the alveolar wall or other pulmonary tissue. In other words, STAS should not be a floating island without any nutrition for survival. A number of studies have demonstrated that STAS, namely a pathologic morphology of loose tumor tissue in air space, is associated with many other clinical characteristics and prognoses of lung cancer. However, thus far, there is no any widely accepted theory to explain the mechanism of survival and development of STAS. More studies are needed to explain the pathologic phenomenon and characterize the nature of STAS. Second, it is unclear whether STAS is a factor of staging system in lung cancer. Taking pleural invasion as an example, this is considered a factor in the features of T2 as defined in the eighth edition of TNM classification of lung cancer by the IASLC.[24] In the IASLC stage grouping, the impact on prognosis is regarded as an important reference for a potential risk factor. However, few studies have determined the role of STAS in the staging system by comparing the prognosis at different stages, and the only evidence is that patients with stage IA positive STAS and patients with stage IB AdC had a comparable RFS and OS.[11] More research is required to identify the accurate role of STAS in

Table 1 Current Studies on the Role of STAS in Lung Cancer

Author, Year	Study Population, n	Histologic Type	Stage	STAS, %	Clinical Factors	Prognosis	Gene Mutation
Kadota et al, 2015[12]	411	AdC	I	38	Lymphovascular invasion, invasive pattern	RR↑ (limited resection group)	
Warth et al, 2015[6]	569	AdC	I-IV	50.6	High stage, invasive pattern, node(+), distant metastasis	OS↓, DFS↓	EGFR(−), BRAF(+)
Shiono et al, 2016[10]	318	AdC	I	14.8	IB stage, lymphovascular invasion, pleural invasion, solid nodules on CT	OS↓, RFS↓	EGFR(−)
Morimoto et al, 2016[13]	444	AdC	I-IV	46.3	Micropapillary component	RR↑, RFS↓	
Dai et al, 2017[11]	544	AdC	I	30.3	Invasive pattern	OS↓, RFS↓	
Uruga et al, 2017[8]	208	AdC	I	47.6	Solid component, vascular invasion, pleural invasion, node(+)	RFS↓	
Lee et al, 2017[9]	316	AdC	I-III	50.6	nodal metastasis, high stage, precence of micropapillary or cribriform component, lymphovascular invasion	OS↓, RFS↓	EGFR(−), ALK RAG,
Toyokawa et al, 2018[7]	276	AdC	I	56.4	Invasive pattern, pleural invasion, tumor size, SUVmax, consolidation/tumor ratio	OS↓, RFS↓	
Kadota, 2017[15]	216	SCC	I-IV	40	High stage, node(+), tumor budding	RR↑, RFS↓	
Lu et al, 2017[17]	445	SCC	I-III	30	High stage, lymphovascular invasion, tumor size, necrosis, nuclear diameter	CIR↑, CID↑	
Yanagawa et al, 2018[18]	220	SCC	I-III	19.1	Lymphovascular invasion	OS and RFS↓ (in stage I)	
Toyokawa et al, 2018[19]	30	SCLC	I-IV	83	No significance	No significance	
Yokoyama et al, 2018[20]	35	Lung pleomorphic carcinoma	I-III	40	Tumor necrosis	OS↓, RFS↓	
Masai et al, 2017[14]	508	All types	I-IV	15	Micropapillary or solid component, lymphovascular invasion, pleural invasion	RR↑	

Abbreviations: AdC = adenocarcinoma; CID = cumulative incidence of cancer-specific death; CIR = cumulative incidence of recurrence; OS = overall survival; RAG = rearrangement; RFS = recurrence-free survival; RR = recurrence rate; SCC = squamous cell carcinoma; SCLC = small-cell lung cancer; SUVmax = maximum standardized uptake value.

the staging system. Finally, does STAS have an influence on the extent of surgical resection or further adjuvant therapy? As mentioned earlier, Kadota et al showed that patients with positive STAS in the limited resection group had a significantly higher recurrence rate than patients in the lobectomy group.[12] It seems that lobectomy is safer when STAS positivity is detected in frozen sections. However, to date, there are no pathologic standards for STAS in frozen sections. Another related potential problem proposed by Walts et al is that frozen section may not be an effective approach for identifying STAS. In their study, STAS was evaluated in frozen section, frozen section control slides, and all additional slides in lung tissue adjacent to tumor. The result showed that STAS incidence was significantly higher in the latter 2 groups, and 23 cases were identified by frozen section among all of 46 cases with STAS; only 2 of the 25 cases were true negative STAS in frozen section. This means that the sensitivity to detect STAS

was 50%, with a 8% negative predictive value for frozen section.[25] Thus, the tricky problem should be resolved that how to evaluate STAS in frozen sections. Furthermore, is adjuvant therapy necessary for patients if STAS is identified in paraffin sections post-operatively? In a large prospective cohort study, vessel invasion was also a poor prognostic factor in non-SCLC, as well as a target for adjuvant chemotherapy.[26,27] Even though STAS has been confirmed to be a predictor of poor prognosis in lung cancer, whether or which postoperative strategy is optimal for patients with positive STAS is still not clear. Future studies are warranted to determine the relationship between STAS and lung cancer treatment.

Conclusions

In summary, the presence of STAS has been detected in AdC, SCC, SCLC, and pleomorphic carcinoma with different incidence levels. STAS has associations with vital clinical and pathologic characteristics, and it is a poor prognostic factor for recurrence and survival in AdC, SCC, and pleomorphic carcinoma. STAS can be considered a new invasive pattern in lung cancer. More evidence is needed to validate and classify STAS and optimize treatment decisions in patients who are STAS-positive.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65:87-108.
2. Amin MB, Tamboli P, Merchant SH, et al. Micropapillary component in lung adenocarcinoma: a distinctive histologic feature with possible prognostic significance. *Am J Surg Pathol* 2002; 26:358-64.
3. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6:244-85.
4. Onozato ML, Kovach AE, Yeap BY, et al. Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. *Am J Surg Pathol* 2013; 37:287-94.
5. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health OrganizationClassification of Lung Tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015; 10:1243-60.
6. Warth A, Muley T, Kossakowski CA, et al. Prognostic impact of intra-alveolar tumor spread in pulmonary adenocarcinoma. *Am J Surg Pathol* 2015; 39:793-801.
7. Toyokawa G, Yamada Y, Tagawa T, et al. Significance of spread through air spaces in resected pathological stage I lung adenocarcinoma. *Ann Thorac Surg* 2018; 105:1655-63.
8. Uruga H, Fujii T, Fujimori S, et al. Semiquantitative assessment of tumor spread through air spaces (STAS) in early-stage lung adenocarcinomas. *J Thorac Oncol* 2017; 12:1046-51.
9. Lee JS, Kim EK, Kim M, et al. Genetic and clinicopathologic characteristics of lung adenocarcinoma with tumor spread through air spaces. *Lung Cancer* 2018; 123:121-6.
10. Shiono S, Yanagawa N. Spread through air spaces is a predictive factor of recurrence and a prognostic factor in stage I lung adenocarcinoma. *Interact Cardiovasc Thorac Surg* 2016; 23:567-72.
11. Dai C, Xie H, Su H, et al. Tumor spread through air spaces affects the recurrence and overall survival in patients with lung adenocarcinoma >2 to 3 cm. *J Thorac Oncol* 2017; 12:1052-60.
12. Kadota K, Nitadori J, Sima CS, et al. Tumor spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. *J Thorac Oncol* 2015; 10:806-14.
13. Morimoto J, Nakajima T, Suzuki H, et al. Impact of free tumor clusters on prognosis after resection of pulmonary adenocarcinoma. *J Thorac Cardiovasc Surg* 2016; 152:64-72.
14. Masai K, Sakurai H, Sukeda A, et al. Prognostic impact of margin distance and tumor spread through air spaces in limited resection for primary lung cancer. *J Thorac Oncol* 2017; 12:1788-97.
15. Kadota K, Kushida Y, Katsuki N, et al. Tumor spread through air spaces is an independent predictor of recurrence-free survival in patients with resected lung squamous cell carcinoma. *Am J Surg Pathol* 2017; 41:1077-86.
16. Kadota K, Nitadori J, Woo KM, et al. Comprehensive pathological analyses in lung squamous cell carcinoma: single cell invasion, nuclear diameter, and tumor budding are independent prognostic factors for worse outcomes. *J Thorac Oncol* 2014; 9:1126-39.
17. Lu S, Tan KS, Kadota K, et al. Spread through air spaces (STAS) is an independent predictor of recurrence and lung cancer-specific death in squamous cell carcinoma. *J Thorac Oncol* 2017; 12:223-34.
18. Yanagawa N, Shiono S, Endo M, et al. Tumor spread through air spaces is a useful predictor of recurrence and prognosis in stage I lung squamous cell carcinoma, but not in stage II and III. *Lung Cancer* 2018; 120:14-21.
19. Toyokawa G, Yamada Y, Tagawa T, et al. High frequency of spread through air spaces in resected small cell lung cancer. *Anticancer Res* 2018; 38:1821-5.
20. Yokoyama S, Murakami T, Tao H, et al. Tumor spread through air spaces identifies a distinct subgroup with poor prognosis in surgically resected lung pleomorphic carcinoma. *Chest* 2018; 154:838-47.
21. Blaauwgeers H, Flieder D, Warth A, et al. A prospective study of loose tissue fragments in non-small cell lung cancer resection specimens: an alternative view to "Spread Through Air Spaces." *Am J Surg Pathol* 2017; 41:1226-30.
22. Lu S, Rekhtman N, Eguchi T, et al. Cases demonstrating spread through air spaces (STAS) reflects invasive growth and not an artifact. *J Thorac Oncol* 2017; 12S:S1137.
23. Kameda K, Lu S, Eguchi T, et al. Can tumor spread through air spaces (STAS) in lung adenocarcinomas be predicted pre- and intraoperatively? *J Thorac Oncol* 2017; 12S:S411-2.
24. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11:39-51.
25. Walts AE, Marchevsky AM. Current evidence does not warrant frozen section evaluation for the presence of tumor spread through alveolar spaces. *Arch Pathol Lab Med* 2018; 142:59-63.
26. Tsuchiya T, Akamine S, Muraoka M, et al. Stage IA non-small cell lung cancer: vessel invasion is a poor prognostic factor and a new target of adjuvant chemotherapy. *Lung Cancer* 2007; 56:341-8.
27. Higgins KA, Chino JP, Ready N, et al. Lymphovascular invasion in non-small-cell lung cancer: implications for staging and adjuvant therapy. *J Thorac Oncol* 2012; 7:1141-7.