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Spread Through Air Spaces (STAS): Where is it in the management of lung cancer?

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Abstract

First identified in 1980 and formally defined by the WHO in 2015, Spread Through Air Spaces (STAS) has attracted much attention in recent years as "the moving finger" affecting the prognosis of lung cancer. The definition of STAS included one or more tumor cells, pathologic micropapillary clusters, and solid nests beyond the edge of the tumor into air spaces in the surrounding lung parenchyma, and separation from the main tumor other than tumor islands. It has been described in lung adenocarcinoma, squamous cell carcinoma, and other primary lung malignancies. The role of STAS in staging and treatment decisions is unclear, although it has been reported to be a contributor to adverse prognosis in lung cancer. This review focuses on the current status, controversies, and perspectives of STAS in lung cancer management in terms of preoperative, intraoperative, and postoperative aspects.

Keywords

Lung cancer; Spread through Air Spaces; Adenocarcinoma.

Introduction

The phenomenon of tumors filling air space within the lung parenchyma was discovered in early 1980 by Kodama et al who considered it a rare and novel biologic behavior of aerogenous metastases [1]. Subsequently, the concept of the aerogenous spread of lung cancer was described with insufficient weight until 2015. The World Health Organization (WHO) classification of lung cancer specifies it as a novel pattern of invasion comparable to vascular or lymphatic invasion and defines 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 [2]. The change in official guidelines means that STAS may have more clinical impact on the management of lung cancer, as it has been reported to seriously influence the treatment outcomes and even influence treatment decisions. This review discusses the current status and controversies of STAS and

focuses on its development and perspectives in the management of lung cancer from pre-operative, intra-operative, and post-operative aspects.

Pathological Diagnosis of STAS

STAS was initially highlighted in lung adenocarcinoma, and subsequent studies have extended it to squamous cell carcinoma [3], sarcomatoid carcinoma [4], and small cell lung cancer [5]. Tumor STAS was composed of three morphological patterns: (1) single cells; (2) micropapillary clusters; (3) solid nests or tumor islands [6]. Also, the morphological features of STAS vary among different types of lung cancer. Clinicopathologists identify and diagnose STAS accordingly.

However, some scholars have raised suspicions about the diagnosis of STAS, suggesting that it is simply an artifact that occurs during the production of pathological sections. Blaauwgeers and his colleagues performed a prospective multi-institutional study to find possible relationships between these free-floating tumor cell clusters and the gross examination procedure [7]. The results surprisingly showed that a majority of the STAS (93%) could be explained by mechanical forces associated with tissue handling. They named it «Spreading through A Knife Surface (STAKS)» [7]. Besides, another study found a significantly higher frequency of STAS in performing thoracoscopic surgery compared to thoracotomy surgery. Song explained the fact that the lung lobes, including the tumor, are always severely compressed during thoracoscopic surgery [8]. The relatively specific definition of the artifact was proposed by Villalba et al. in 2021, including clusters of cells randomly scattered on tissue or at the edges of tissue sections, clusters of cells with jagged edges, linear strips of cells lifted from the alveolar wall, and isolated clusters of tumor cells away from the primary tumor [9]. On the contrary, Metovic and his colleagues conducted an interesting prospective study in which fresh surgical lung specimens were sectioned with a fresh clean blade for each cut. The results showed no difference in the occurrence of STAS between freshly cut and fixed corresponding samples, and between the samples before and after the blade crossed the tumor [10]. Gross et al. reviewed patients who underwent limited resection, had STAS in limited resection specimens and underwent additional resection. They found that STAS was also observed in additional resected specimens processed using different knives, which supports the idea that STAS is an in vivo phenomenon [11].

The presence of artifacts does not mean that STAS is not an objective pathological manifestation. Artifacts do not explain the fact that STAS is an independent risk factor affecting the prognosis of lung cancer. However, we acknowledge that the occurrence of STAS is probably overestimated. A more standardized sample handling process and artifact exclusion definitions possibly reduce the impact of artifacts on the diagnosis of STAS.

Qualitative and Semiquantitative Assessment

The criteria for STAS differ in various research, from a single cell to small nests of cells (>5 tumor cells) and the incidence of STAS also varies considerably between studies enrolling patients with the same stage of lung adenocarcinoma [5,12,13]. The classification and qualitative assessment of STAS based on morphological patterns meaning that a single tumor cell observed beyond the margin of the main tumor

are capable of a positive diagnosis of STAS. However, it's not sufficient. Despite careful surgical specimen processing and artifact differentiation, single-cell STAS was the common morphologic type of artifact produced by a prosecuting knife [14].

Thus, several studies have stratified STAS by the quantity and the diffusion area of STAS from the main tumor. Warth and his colleagues proposed morphological criteria for limited and extensive STAS. The limited STAS is defined as a cluster of tumor cells spreading through the airspace less than three alveoli away from the main tumor, and beyond three alveoli is considered extensive STAS [15]. Another research demonstrated that STAS was graded as I when all tumor clusters were present within 2500μm from the tumor margin and graded as II when any tumor cluster exceeded this distance [16]. In 2017, Uruga and his colleagues first proposed a semi-quantitative assessment of STAS, classifying STAS as no STAS, low STAS (1-4 single cells or clusters of STAS), and high STAS (≥5 single cells or clusters of STAS) [17]. These assessments are essential to guide risk stratification and subsequent studies of STAS.

Clinical Prognosis of STAS

A large number of studies focused on the impact of lung cancer combined with STAS on prognostic indicators such as Recurrence-Free Survival (RFS) and overall survival (OS). Kadota et al. in 2015 first indicated that patients with STAS-positive stage I lung adenocarcinoma had a significantly higher risk of recurrence than STAS-negative patients (5-years RFS 57.4% versus 89.1%; $p<0.001$), and the presence of STAS was associated with a higher risk of distant ($p=0.035$) and local recurrence ($p=0.001$) [6]. Subsequently, multiple studies including various histological types and different stages of lung cancer have found a negative prognostic effect of STAS. A retrospective study by Morimoto and colleagues included patients with stage I-IV lung adenocarcinoma and showed a significantly lower 5-years RFS in STAS-negative patients [18]. Lu et al. found a significantly higher cumulative incidence of distant and local area recurrence and lung cancer-specific death in patients with STAS-positive lung squamous cell carcinoma, despite no statistically significant difference in OS [19]. The absence of significant differences in OS may be related to the continuous advancement in lung cancer treatment. In addition to this, the same poor prognostic effect of STAS was seen in atypical carcinoid, large cell neuroendocrine carcinoma, and small cell carcinoma of the lung in Aly et al. study [20]. Current research on the role of STAS in lung cancer is shown in Table 1.

Besides, multiple retrospective clinical evidence suggests that lobectomy in patients with STAS-positive stage T1 lung adenocarcinoma may have better survival outcomes than sublobar resection. Kadota et al. reported a higher rate of recurrence ($p=0.010$) and locoregional recurrence ($p=0.002$) in patients with STAS who underwent limited resection than in those who underwent lobectomy [12]. Another study indicated that STAS was a significantly poorer prognostic factor in the sublobar resection group, but not in the lobectomy group [21]. An interesting propensity score–matched analysis by Eguchi et al. also found that sublobar resection was an independent risk factor for recurrence and lung cancer-specific death in patients with STAS. Furthermore, in patients with STAS who underwent limited resection, wider margins may not prevent recurrence in these patients [22].

Table 1: Current research on the role of STAS in lung cancer.

Study/ years	Study population	Histologic type	Stage	Criteria of STAS	% STAS	Clinicopathological factors	Prognosis
[39]	73	ADC	pI-III	NR	71.20%	histological grade, lepidic pattern	RFS↓
[40]	61	ADC	pI-III	tumour cell clusters and single tumor cells	55.70%	histological grade, lymphovascular invasion	RFS↓OS↓
[41]	121	IMA	pI-III	solid cell nests (≥5 tumor cells)	65.40%	consolidative morphology, T and N stage	DFS↓OS↓
[42]	241	SCC	pI-IV	free-floating cell clusters	35.70%	T and N stage, pleural invasion, histopathological subtype, tumor necrosis, vasculolymphatic invasion	OS↓
[43]	795	ADC	pI-III	tumor cells within alveolar spaces in the lung parenchyma	25.30%	pathologic tumor size	RFS↓
[44]	506	ADC	pI	micropapillary clusters, solid nests, or single cells	40.30%	NR	RFS↓
[45]	609	ADC	pI-III	a single cell, small cluster, or large cell nest	48.10%	NR	RFS↓
[46]	803	NSCLC	pI-IV	a single cell, small cluster, or large cell nest	46%	STAS subtypes	RFS↓OS↓
[47]	635	NSCLC	pI-III	small clusters of tumor cell nests	44%	epithelial-mesenchymal transition	RFS↓OS↓
[48]	132	IMA	pI-III	small solid cell nests (at least five tumor cells)	72.30%	age, smoking history, T stage, lymph node metastasis, consolidative morphologic type	OS↓
[49]	424	ADC/SCC	cI-IV	a single cell, small cluster, or large cell nest	222/424	clinic stage	DFS↓OS↓
[50]	217	ADC	cIA	small cluster, or large cell nest	15.70%	NR.	OS↓
[51]	487	NETs	pI-III	more than one tumor cell nest	26%	NR.	CIR↑LC-CID↑
[52]	76	ADC	cIII	a single cell, small cluster, or large cell nest	60.50%	NR.	RFS↓OS↓
[53]	735	ADC	cI	small clusters	33.60%	lymphovascular invasion, sex, nodal positivity, pathological stage	RFS↓OS↓
[54]	752	ADC	pIA	single cells, micropapillary clusters, solid nests	29.90%	sex, T stage	RFS↓ (Sublobar resection), OS↓
[55]	848	NSCLC	pI	tumor clusters, (at a distance of at least 0.5 mm)	16.40%	lymphovascular and pleural invasion, sex, smoking history, CEA, tumor size	RFS ↓
[56]	1497	ADC	pI	clusters, solid nests, single cells	NR.	NR.	NR.
[57]	327	ADC	pI	single tumor cells/clusters	58.40%	histological differentiation, CEA	RFS↓
[58]	35	LPC	cI-III	single cells, micropapillary clusters, solid nests	40%	tumor necrosis	RFS↓, OS↓
[59]	514	NSCLC	cIA	tumor clusters, (at a distance of at least 0.5 mm)	20.20%	age, lymph node metastasis, sex	RFS↓ (Sublobar Resection), OS↓ (Sublobar Resection)
[60]	220	SCC	cI-III	free-floating cell clusters	19.10%	NR	RFS↓, OS↓ (stage I)

[61]	276	ADC	pI	at least 1 single cell or clusters	55.40%	Pleural invasion, tumor size, CEA	RFS↓, OS↓
[62]	508	NSCLC	cI-III	single cells, micropapillary clusters, solid nests	15%	lymphovascular and pleural invasion, male, smoking history	RR↑
[3]	216	SCC	cI-III	free-floating cell clusters	40%	NR	RFS↓
[63]	544	ADC	cIA	single-cell, micropapillary cluster, or solid nest	30.30%	sex	NR
[64]	208	ADC	cI	at least 1 tumor cells	47.60%	lymphovascular and pleural inasion, tumor size	RFS↓
[65]	445	SCC	cI-III	tumor cell nests	30%	lymphatic and vascular invasion, Ki-67	RFS↓
[66]	560	ADC	cI-III	single-cell, micropapillary cluster, or solid nest	50.60%	sex, pathological stage, nodal positivity, distant metastasis	DFS↓, OS↓
[6]	411	ADC	cI	small clusters	38%	lymphovascular invasion	NR
[67]	261	ADC	cI-II	Tumor Islands	22.20%	Smoking history, high nuclear grade	RFS↓

ADC: Adenocarcinoma; **IMA:** Invasive Mucinous Adenocarcinoma; **SCC:** Squamous Cell Carcinoma; **NSCLC:** Non-Small Cell Lung Cancer; **NETs:** Neuroendocrine Tumors; **LPC:** Lung Pleomorphic Carcinoma; Recurrence-free survival; **OS:** Overall survival; **DFS:** Disease-free survival; **CIR:** Cumulative Incidence of Recurrence; **LC-CID:** Lung cancer-specific cumulative incidence of death.

Preoperative Prediction of STAS

The close association between STAS and lung cancer prognosis has motivated researchers to explore the preoperative prediction of STAS. Medina et al. performed an interesting study examining the relationship between preoperative bronchial cytology and STAS, although the results showed that bronchial cytology did not identify the occurrence of STAS [23]. Additional studies have identified the association between various radio-morphology features of lung cancer and the presence of STAS.

The most frequently studied features associated with STAS include diameter, Consolidation/Tumor Ratio (CTR), and the percentage of the solid component. The larger the diameter of the tumor, the higher the incidence of STAS. De Margerie-Mellon et al. revealed that the diameter of STAS-positive tumors, including the overall mean diameter and the mean and long-axis diameters of the solid fraction, was significantly larger than that of STAS-negative ones [24]. Zhang et al. presented that tumor diameter and maximum solid component diameter are important predictors of STAS in stage cIA lung adenocarcinoma (≤3cm) [25]. However, the finding was not revealed in the study by Kim et al [26]. This may be related to the small amounts of patients with T3 and T4 stages. An increase in the proportion of solid components or the CTR is also a risk factor for predicting the presence of STAS. Kim et al. observed that STAS is more usual in solid tumors than in part-solid or ground-glass lesions ($p<0.001$). Toyokawa et al. observed that the absence of Ground-Glass Opacity (GGO) was independently associated with the STAS phenomenon ($p <0.01$) [27]. Similarly, Qi et al. explored the best CT sign for predicting STAS in small-sized lung adenocarcinoma(≤2 cm), and results showed that CRT has the best potential for predicting STAS [28]. Interestingly, STAS may not be present in pure GGO lesions, a phenomenon occurring in some studies [26,29]. Another point that caught our eye was the confrontation between the GGO and STAS. Zhong et al. observed that the prognostic role of STAS abruptly disappears in stage I lung adenocarcinoma with GGO. It has a comparable recurrence rate and ($p=0.65$) survival rate regardless ($p=1$) of the presence or absence of STAS, indicating that GGO

is a more reliable prognostic predictor for stage I lung adenocarcinoma [29]. In addition, the presence of cavitation, lobulation, air bronchogram, and vascular convergence also has been widely discussed as morphological features that have implications for the presence of STAS [24-26].

Qualitative CT features are inevitably limited by individual interpretation and image resolution. Therefore, many scholars have attempted to predict STAS by radionics-based models, which enable image features to be extracted and translated into quantitative information by specialized software. Chen et al. and Jiang et al. delineated and then segmented the tumor-extracting radiomic features for statistical analysis [13,30]. The area under the working characteristic curve (AUC) for the subjects was 0.69 and 0.75, respectively, indicating the sound predictive performance of the model for STAS. It is worth mentioning that both radiological models integrate tumor radiological features and clinical factors to improve the prediction. The radiomics features around the tumor also require attention. Liao et al. integrated different peritumoral radiomic signatures and obtained a model AUC of 0.87, achieving a better performance in STAS than the former [31]. Currently, radiomics seems to be the best predictive tool with objectivity and stability, but it is still hardly applicable to daily clinical practice and further research is needed.

Intraoperative Evaluation of STAS

If STAS can be accurately identified in intraoperative Frozen Sections (FS), a more appropriate surgical approach can be considered. The initial results of the study seemed discouraging. Walts et al. conducted a study on whether STAS could be reliably identified in FS, stratifying patients undergoing lobectomy or sublobar resection. The results showed an unacceptably low sensitivity of FS for STAS detection (50%), thus concluding that intraoperative pathological detection of STAS does not help guide the surgical approach [32]. Similar results were demonstrated in a retrospective cohort by Zhou et al [33]. In subsequent reports, the feasibility of assessing STAS in FS was improved. Although the sensitivity was still low, a decent specificity and accuracy were shown in the study by Villalba et al (44%,91%,71%) [34]. In addition to this, an important finding reported by Eguchi et al was that pathologists were able to identify STAS on intraoperative FS with greater sensitivity and specificity (71%, 92%) [22]. To take a step further, Kimura et al. proposed that STAS is associated with the novel Nakayama-Higashiyama (N-H) imprint cytological classification, and N-H classification as an intraoperative predictive marker of STAS [35].

A series of consecutive studies have demonstrated the low sensitivity and limited predictive value of intraoperative pathology for STAS. Intraoperative FS evaluation in conjunction with preoperative imaging histology or other pathological features may improve STAS sensitivity and detection rates.

Postoperative Treatment of STAS-Positive Lung Cancer

STAS is a dangerous sign in the prognosis of lung cancer, but current studies on STAS and adjuvant therapy were scarce. Chen et al. performed a subgroup analysis of survival in patients with stage IA STAS-positive lung adenocarcinoma who underwent limited resection and showed a survival advantage for patients receiving adjuvant chemotherapy (OS, p=0.007; Disease-free survival (DFS), p=0.005) [36]. Xie and his colleagues further confirmed that adjuvant chemotherapy facilitates long-term survival in patients with

stage I STAS-positive lung adenocarcinoma who underwent lobectomy [37]. The latest EMSO clinical practice guidelines have already stated that adjuvant chemotherapy or radiotherapy should be considered for patients with resected stage IB disease and primary tumors >4 cm [38]. Compared with the clear emphasis on standardized regular post-operative reviews, whether patients in stage IA non-small cell lung cancer (NSCLC), should receive chemotherapy or radiotherapy after surgery remains controversial. More studies are still needed to prove whether STAS can be an indicator for postoperative chemotherapy in patients with stage IA. In addition to this, whether STAS-positive can benefit more from postoperative adjuvant therapy in different stages of lung cancer also needs more research.

Discussion

In conclusion, STAS was identified in diverse histological subtypes of lung cancer and is an essential prognostic feature independent of tumor stage and growth pattern. Because of the great inconsistency between studies, STAS is currently similar to vascular invasion and draws the attention of clinicians only as a danger sign. Imaging histology combined with intraoperative evaluation is likely to identify STAS more accurately, but it remains uncertain whether the surgical approach should be changed accordingly. More consistent criteria for STAS definition, exclusion, and stratified assessment are required to improve the consistency and accuracy of diagnosis in the future. More large prospective studies may prove the importance of STAS, and in the future, STAS may be capable of influencing the staging and management of lung cancer as pleural invasion does.

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