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Spread Through Air Spaces (STAS) in Pulmonary Adenocarcinoma: Prognostic Meaning and Surgical Implications

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STAS, pulmonary adenocarcinoma, surgical prognosis

ABSTRACT
Spread Through Air Spaces (STAS) is a pattern of cancer cell invasion found in pulmonary adenocarcinoma and has been identified as a significant independent prognostic factor. The presence of STAS is closely related to an increased risk of local recurrence and a decrease in survival rates, especially in patients undergoing limited resection. This research aims to review the literature related to the prognostic significance and surgical implications of STAS, as well as to evaluate preoperative and intraoperative diagnostic approaches such as CT scans, PET/CT, frozen section, and radiomics. The findings suggest that although the definitive diagnosis of STAS can only be established postoperatively, the development of preoperative predictive technologies is critical in supporting more informed clinical decision-making. It is hoped that STAS can be included in international clinical guidelines to assist in the determination of individualized therapy strategies for lung cancer patients.

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INTRODUCTION

Spread through air spaces (STAS) was first introduced by Kadota et al. in 2015 as a phenomenon of airborne lung cancer spread (Jia et al., 2020; Kadota et al., 2019). In 2000, Giraud et al. defined this phenomenon as *aerogenic diffusion*, describing the presence of cancer cells that reside freely within the lumen of the alveoli (Giraud et al., 2000). The terminology of STAS has been recognized by the World Health Organization (WHO), which officially recognizes it as an invasive mechanism for the spread of microcapillaries, dense nests, and/or single cancer cells into the air spaces of the lung parenchyma beyond the edge of the main tumor (Travis et al., 2015; Mino-Kenudson, 2020).

STAS has been shown to be a predictor of poor prognosis and is associated with local-regional recurrence after limited resection surgery in adenocarcinoma cases, as well as in other types of lung carcinoma, such as squamous cell carcinoma, neuroendocrine neoplasms, and pleomorphic carcinoma (Kadota et al., 2019; Gross et al., 2021). These findings prompt greater attention to the role of STAS in clinical decision-making, especially in determining the optimal type of surgical procedure. A number of studies suggest that the presence of STAS can be a determining factor in whether *sublobar resection* is sufficient or a *lobectomy* is necessary to reduce the risk of recurrence (Takahashi et al., 2019; Masai et al., 2017). In addition, the WHO has established that the presence of STAS excludes the diagnosis of *adenocarcinoma in situ* (AIS) and *minimally invasive adenocarcinoma* (MIA), signifying the importance of STAS detection in the classification and stratification of modern lung cancer (Travis et al., 2015; Mino-Kenudson,2020).

The pathophysiology of lung cancer is highly complex and not yet fully understood. One theory states that repeated exposure to carcinogens, such as cigarette smoke, can cause dysplasia of the pulmonary epithelium (Kumar & Kumar, 2022; Siddiqui et al., 2025). If this exposure is continuous, it may result in genetic mutations that interfere with protein synthesis. This disruption then interferes with the normal cell cycle and triggers the process of carcinogenesis (cancer formation). Some of the most common genetic mutations involved in the development of lung cancer are found in *small cell lung cancer* (SCLC): mutations in the MYC, BCL2, and p53 genes, and in *non-small cell lung cancer* (NSCLC): mutations in EGFR, KRAS, and p16 (Lindeman et al., 2018).

About 80% of all lung cancer cases are classified as NSCLC, with *adenocarcinoma* being the most dominant histological type (Kumar & Kumar, 2022). In the 2021 WHO Classification of Lung Tumors, the classification system of pulmonary adenocarcinoma subtypes essentially continues to follow the guidelines established since 2015. Invasive *adenocarcinoma* is categorized into six main types: *minimally invasive adenocarcinoma* (MIA), invasive non-mucinous adenocarcinoma, *colloid adenocarcinoma*, *fetal adenocarcinoma*, and *enteric-type adenocarcinoma*. These six types are distinguished from glandular precursor lesions, such as *atypical adenomatous hyperplasia* (AAH) and *adenocarcinoma in situ* (AIS). Among these subtypes, invasive non-mucinous adenocarcinoma is the most common type. These tumors consist of malignant epithelial cells that exhibit glandular differentiation, both morphologically and by immunohistochemistry. However, this type of adenocarcinoma does not meet the criteria of other, more specific subtypes (Nicholson et al., 2022).

Morphologically, invasive non-mucinous adenocarcinoma can display growth patterns in the form of *lepidic*, *acinar*, *papillary*, and *micropapillary* types (Solis et al., 2012; Lu & Xu, 2023). In tumors with pure solid growth, the diagnosis of adenocarcinoma requires additional evidence from immunohistochemistry, such as TTF-1 or Napsin A, or from histochemical examination (Siddiqui et al., 2025; Nicholson et al., 2022).

In the latest classification, invasive measurements have become important, especially for non-mucinous adenocarcinoma with a *lepidic* pattern. This is because TNM staging systems consider only the size of the invasive tumor component, not the overall size of the tumor mass. In addition, the WHO has introduced a grading system to assess the degree of malignancy in invasive adenocarcinoma (Nicholson et al., 2022).

Table 1. Degree of Invasive Adenocarcinoma of The 2021 WHO Classification of Lung Tumors (Nicholson et al., 2022)

Degree	Description
Degree 1 (good differentiation)	Dominated by lepidic patterns, with no or < 20% of high-degree patterns
Degree 2 (medium differentiation)	Dominated by an asinar or papillary pattern, with no or < 20% of the high degree pattern
Degree 3 (poor differentiation)	Tumors with ≥20% of the high-degree pattern, regardless of the dominant pattern

Source: Adapted from Nicholson et al. (2022), The 2021 WHO Classification of Lung Tumors, Journal of Thoracic Oncology, 17(3), 362–387

The occurrence of spread through air spaces (*STAS*) is not affected by macroscopic specimen handling procedures, such as postoperative tissue cutting or manipulation. In pulmonary *adenocarcinoma*, *STAS* generally forms in three main morphological patterns: micropapillary structures, dense clusters of tumor cells (*solid nests*), and single tumor cells that are not attached to each other (*discohesive single cells*) (Travis et al., 2015; Nicholson et al., 2022).

STAS is recognized as one of the important mechanisms for the spread of cancer cells, especially in early-stage lung *adenocarcinoma*. Several studies have shown that the presence of *STAS* has a significant impact on the likelihood of recurrence following resection of stage I tumors (Chen et al., 2017).

In pulmonary *adenocarcinoma*, *STAS* is now acknowledged as a crucial feature in pathological assessment according to the latest WHO classification. If *STAS* is detected in patients undergoing *sublobar resection*, this may indicate the need for a *lobectomy* as a follow-up procedure, since the presence of *STAS* in limited resections is associated with a higher risk of recurrence compared to *lobectomy (ResearchGate, 2025)*.

The presence of *STAS* is consistently associated with poorer clinical outcomes, not only in pulmonary *adenocarcinoma*, but also in nearly all major histological subtypes of lung cancer that have been studied. The adverse impact of *STAS* on prognosis is even more pronounced in patients who undergo limited resection compared to those who undergo *lobectomy*. Because *STAS* is considered a pattern of tumor spread (rather than a primary structural component of the tumor mass), it is not quantified as a percentage of histological patterns nor is it included in tumor size measurements for staging purposes (Travis et al., 2015; Nicholson et al., 2022).

STAS is defined as the presence of tumor cells within the pulmonary airspaces located outside the main edge of the tumor (Nicholson et al., 2022). This mechanism exhibits the biological property wherein cells can detach from the main tumor group and spread independently through the air (Mino-Kenudson, 2020). Onozato et al. identified *tumor islands*—large clusters of tumor cells that appear separate within the alveolar space but, through 3D reconstruction, are shown to be connected to the main tumor mass. These structures closely resemble the *solid nest* type of *STAS*, especially the larger formations (Onozato et al., 2013).

It is important to distinguish true *STAS* from tissue preparation artifacts, which can mimic tumor spread but do not reflect actual biological processes (Nicholson et al., 2022). Features that favor artifacts over genuine *STAS* include: randomly located clusters of tumor cells with irregular edges, usually present at the tissue cut's edge or outside the field of the microscopic slide; lack of a continuous pattern of spread from the tumor margin to the farthest part of the airspace where tumor cells are found; presence of pneumocytes or bronchial cells with benign cytology and/or cilia, indicating normal structure; and rows of cells that appear lifted from the alveolar wall rather than actively infiltrating (Kadota et al., 2019; Mino-Kenudson, 2020; Garlin-Politis et al., 2024).

Using these criteria, researchers have been able to distinguish true *STAS* from artifacts with high consistency, as evidenced by an evaluation study of selected images that demonstrated an average kappa value of 0.857, indicating an excellent level of reproducibility (Nicholson et al., 2022). In contrast, vascular invasion is specifically defined as the infiltration of tumor cells into the lumen of an artery or vein, located either within the tumor or in the surrounding tissue (Nicotra et al., 2024).

STAS has been extensively studied and identified as a predictor of poor prognosis, associated with local-regional recurrence after resection surgery, particularly in *adenocarcinoma* and other lung carcinomas such as squamous cell carcinoma, neuroendocrine neoplasms, and pleomorphic carcinoma (Kadota et al., 2019; Gross et al., 2021). Research by Kadota et al. (2019) demonstrated that limited resection in *STAS*-positive stage I lung *adenocarcinoma* resulted in higher locoregional recurrence rates compared to *lobectomy*.(2) Additionally, studies by Masai et al. (2017) highlighted the prognostic impact of *STAS* on survival outcomes, emphasizing its role in surgical decision-making.

While previous studies have established *STAS* as a prognostic factor, this research aims to synthesize the latest advancements in preoperative and intraoperative diagnostic techniques,

such as CT scans, PET/CT, radiomics, and frozen section analysis, to predict *STAS*. Furthermore, it explores the potential integration of *STAS* into international clinical guidelines—a topic still under investigation. The urgency of this research lies in the clinical challenges that *STAS* presents: definitive diagnosis is currently possible only postoperatively, delaying optimal treatment decisions. With lung cancer remaining a leading cause of cancer deaths globally (Sung et al., 2021), improving preoperative detection of *STAS* is critical for guiding surgical strategies (e.g., *sublobar resection* vs. *lobectomy*) and planning adjuvant therapy, ultimately enhancing patient outcomes.

This research aims to examine in depth the role of spread through air spaces (*STAS*) as a prognostic factor in pulmonary *adenocarcinoma*, focusing on its implications for surgical decisions and patient survival. In addition, this study seeks to evaluate the latest diagnostic methods, such as CT scans, PET/CT, radiomics, and frozen section examinations, for detecting *STAS* pre- and intraoperatively. Thus, this study is expected to provide evidence-based recommendations for the integration of *STAS* into international clinical guidelines, to support more individualized and effective therapies.

METHOD

This research utilizes a literature review approach by tracing and analyzing various relevant scientific publications related to the phenomenon of spread through air spaces (*STAS*) in pulmonary *adenocarcinoma*. Data sources were obtained from international journal articles published between 2000 and 2025 through databases such as PubMed, Scopus, and Google Scholar, using the keywords "*STAS*", "*lung adenocarcinoma*", "*prognosis*", and "*surgical implications*". Inclusion criteria comprised studies addressing the pathology, diagnosis, prediction, and clinical impact of *STAS*, including retrospective, prospective, and meta-analysis studies. The collected data were analyzed descriptively to develop a comprehensive understanding of the prognostic significance of *STAS* and its implications for surgical decision-making.

RESULTS AND DISCUSSION

Diagnosis and Implications of Surgery

According to Global Cancer Statistics In 2020, lung cancer remains one of the leading causes of cancer deaths in the world (Sung et al., 2021). A number of studies have proven that STAS (Spread Through Air Spaces) is an independent risk factor for poor prognosis in lung cancer patients, as well as a significant effect on Recurrence-free survival (RFS) and Overall Survival (OS) postoperative. Therefore, accurately predicting the status of STAS before surgery is essential in determining the optimal surgical plan (Wang et al., 2023).

Compared to sublobectomy, lobectomy is known to provide better prognosis outcomes for patients with STAS (T et al., 2019). However, the definitive diagnosis of STAS can usually only be established through postoperative pathological examination, so the determination of therapy is often delayed (Wang et al., 2023).

Over the past few years, various methods have been developed to detect STAS preoperatively, such as bronchoscopy, Percutaneous transthoracic needle biopsy (PTNB), and intraoperative frozen preparations examination (Frozen section/FS). Unfortunately, each method has limitations: Preoperative bronchial cytology provides only low accuracy in detecting STAS. PTNB has low sensitivity and is at risk of causing complications such as infection, pneumothorax, vascular injury, or hematoma. Intraoperative frozen preparations are time-limited and often make it difficult for pathologists to identify STAS definitively (Cao et al., 2021; Zhou et al., 2022; Xu et al., 2024; Medina et al., 2020).

The presence of STAS can be found from the examination of frozen sections, permanent sections (Zhou et al., 2022). Role Frozen section (FS) to detect STAS. Studies conducted by Kameda et al and Walts et al showed that the sensitivity of FS in detecting STAS was around 50–71%, specificity was 92–100%. If STAS is seen in FS, it is likely (92–100%) that it will also be seen in permanent preparations, however, the current evidence is not strong enough to recommend routine use of FS to detect STAS (Travis et al., 2018).

STAS is a typical tumor invasion pattern in pulmonary adenocarcinoma and is a strong prognostic factor, especially in patients undergoing limited resection. A retrospective study conducted by Cao et al in 2021, micropapillary/solid histological subtypes, Intra tumoral budding (ITB), as well as desmoplasia in PTNB have the potential to be promising histological biomarkers to predict the presence of STAS in cases of pulmonary adenocarcinoma and assist surgeons in determining the most appropriate therapy strategy for each patient (Cao et al., 2021).

As technology develops, various noninvasive imaging methods that are able to reflect tumor characteristics as a whole are beginning to be researched. Several studies have shown that the morphological characteristics of lung CT scans can correlate with the presence of STAS. In a retrospective study by Kim et al, STAS was more commonly found in pulmonary adenocarcinomas with solid nodules, and tumor consolidation ratios (Consolidation tumor ratio/CTR) became an independent predictor with a threshold of 90%. At this value, the sensitivity to detect STAS reached 89.2%, and the specificity was 60.3% (Kim et al., 2018).The absence of ground-glass opacity is reported to be related to STAS. This modality is unfortunately subjective and varies between studies, so CT scan-based STAS predictions still need further validation (Wang et al., 2023).

18-fluorine-fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) not only describes the morphology of the tumor, but also reflects its metabolic activity.(29) Several studies have shown that parameters such as SUVmax, total lesion glycolysis (TLG), and tumor/liver FDG uptake ratio have predictive values for STAS. Multivariate prediction models show the specificity of this modality up to 88.6% and an accuracy of 71.1%. However, most studies are retrospective and have not been validated, so more research is needed to confirm the role of PET/CT in STAS prediction and patient prognosis (Volpi et al., 2018).

Radiomics is a technique that extracts quantitative data from CT or MRI images to uncover the biological characteristics of tumors. Several studies have shown that radiomics have the potential to predict STAS preoperatively in pulmonary adenocarcinoma. Chen et al. and Jiang et al. used predictive models based on radiomic features and machine learning, with AUCs ranging from 0.63–0.75, indicating moderate predictive values. Studies by Zhuo et al. and Qi et al. show high accuracy, with AUCs of up to 0.99, especially when combining tumor features, surrounding tissues, and clinical data. Despite the promise, the use of radiomics is still limited by a complex and time-consuming process, so its application in clinical practice still requires further validation (Wang et al., 2023).

STAS has been identified as a distinctive and clinically meaningful tumor invasion pattern in pulmonary adenocarcinoma (Chen et al., 2017). The presence of STAS has been shown to correlate with higher recurrence rates, poorer prognosis, as well as influencing surgical decisions, especially in cases of limited resection (Herba et al., 2025). As understanding of morphology and its mechanism of spread develops, STAS is increasingly recognized as an important independent prognostic factor (Travis et al., 2015; Herba et al., 2025; Travis et al., 2024).

Although postoperative diagnosis through histopathological examination remains the gold standard for identifying STAS, a variety of preoperative and intraoperative approaches are currently being researched (Zhou et al., 2022; Herba et al., 2025). This includes the use of CT

scans, PET/CT, PTNB, and frozen preparation examinations, however, most of these approaches still have limitations in accuracy and reproducibility (Wang et al., 2023).

Suggestions for future research, development of fast and accurate intraoperative detection methods to detect STAS in real-time. Identification of STAS-specific molecular or genetic biomarkers that can be detected through blood or tissue biopsy. Implementation of a multi-flashlight prospective study to validate the predictive value of imaging methods and clinicopathological models on STAS. Further evaluation of the role of STAS morphological subtypes (micropapillary, solid nest, single cell) in influencing recurrence types and therapeutic responses.

It is hoped that in the future, STAS can be officially included in international clinical guidelines (e.g. NCCN or WHO) as one of the determining factors for clinical decision-making. This can help clinicians design more individualized treatment strategies, particularly in determining the optimal type of surgery and the potential need for adjuvant therapy, even in the early stages.

CONCLUSION

Based on a recent literature review and clinical evidence, spread through air spaces (*STAS*) in pulmonary *adenocarcinoma* is shown to be a significant independent prognostic factor, contributing to local recurrence as well as decreased patient survival, especially in cases managed with limited resection. Although the definitive diagnosis of *STAS* still relies on postoperative histopathological examination, various preoperative and intraoperative approaches—such as CT scan, PET/CT, radiomics, and frozen section analysis—are continually being developed to improve prediction accuracy. Moving forward, the integration of *STAS* into official clinical guidelines is necessary so that lung cancer management strategies, including the selection of surgical techniques and considerations for adjuvant therapy, can become more personalized, precise, and evidence-based.

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