Review Article

Advances in the prediction of spread through air spaces with imaging in lung cancer: a narrative review

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Background and Objective: In 2015, the World Health Organization (WHO) officially defined spread through air spaces (STAS) as the fourth type of lung adenocarcinoma (ADC) invasion. STAS is recognized to have effects on the survival rate and the prognosis of patients who have received lung cancer surgery. Given that postoperative pathological diagnosis is the gold standard for STAS diagnosis, but the pathological findings cannot guide the selection of preoperative surgical plan, it is essential to accurately predict STAS before surgery to achieve optimal outcomes.

Methods: A comprehensive, non-systematic review of the latest literature was carried out in order to define the advancement of imaging in predicting STAS. PubMed database was being examined and the last run was on 27 June 2022.

Key Content and Findings: In this review, the definition and the clinical significance of predicting STAS for lung cancer patients were being discussed. By summarizing the STAS prediction efficacy from imaging-related research, the results suggest that computed tomography (CT), 18-fluorine-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT), radiomics and deep learning (DL) are of great value in predicting STAS.

Conclusions: STAS is an important invasion type of lung cancer, affecting the survival prognosis of patients. Preoperative CT and ^{18}F-FDG PET/CT have certain value in predicting the status of STAS, assisting clinicians in selecting an optimal surgical approach and postsurgical treatment. The prediction of STAS based on radiomics and DL can represent a future research direction.

Keywords: Lung cancer; spread through air spaces (STAS); imaging; prediction

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Introduction

According to Global Cancer Statistics 2020, lung cancer remains one of the leading causes of cancer death (1). Studies have proved that spread through air spaces (STAS) is an independent risk factor for poor prognosis in lung cancer patients and affects recurrence-free survival (RFS) and overall survival (OS) after surgery. Accordingly, accurate prediction of STAS status before the operation is of great significance for the selection of surgical plan for lung cancer patients. Compared with sublobectomy, lobectomy can improve the prognosis of patients (2).

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Table 1 The search strategy summary

Items	Specification
Date of search	June 27, 2022
Databases and other sources searched	PubMed
Search terms used	("STAS") AND ("lung cancer" OR "CT" OR "^{18}F-FDG PET/CT" OR "radiomics" OR "predicted" OR "prognosis")
Timeframe	2000–2022
Inclusion and exclusion criteria	All study types and reviews, written in English
Selection process	Yun Wang independently conducted the search; all the authors contributed to the final version of the paper

Postoperative pathology is the gold standard for diagnosing STAS, but the selection of clinical treatment regimens for STAS patients lacks timeliness. Over the years, significant emphasis has been placed on diagnosing STAS in lung cancer by preoperative bronchoscopy, percutaneous transthoracic needle biopsy (PTNB) and intraoperative frozen section (FS) pathology. Preoperative bronchial cytology exhibited a limited ability to predict the STAS status of tumors. Besides, percutaneous biopsy yielded a low sensitivity for the diagnosis of STAS and can cause local infection, pneumothorax, vascular injury, hematoma and other complications. The time for intraoperative FS pathological diagnosis of STAS is limited, and it is often challenging for pathologists to definitively diagnose the existence of STAS (3-5). Therefore, noninvasive imaging methods that comprehensively reflect tumor characteristics have been widely researched. This article reviews the recent imaging-related findings on predicting STAS in lung cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2593/rc).

Methods

A non-systematic review of the latest literature to predict the status of STAS in lung cancer patients was carried out. Relevant articles in English available in the PubMed database as at 27 June 2022 were included. Search terms included ("STAS") AND ("lung cancer" OR "CT" OR "^{18}F-FDG PET/CT" OR "radiomics" OR "predicted" OR "prognosis") (*Table 1*).

Discussion

Definition

In 2013, Onozato *et al.* (6) proposed the definition of "tumor islands" as clusters of free tumor cells in the alveolar spaces. Studies have shown that they are associated with a poor 5-year RFS rate for patients with lung adenocarcinoma (ADC). Active intervention is needed for patients with "tumor islands". In 2015, Kadota *et al.* (2) did a study on 411 patients with stage I lung ADC 2 cm or less and defined the STAS, which indicated the presence of tumor cells within the air spaces in the lung parenchyma beyond the edge of the main tumor in the form of micropapillary clusters, solid nests, or single cells. Warth *et al.* (7) retrospectively analyzed the data of 569 patients with stage I-IV lung ADC and found that approximately half of the lung ADC had focal or diffuse STAS and tumor cell clusters with a length of less than 3 alveolar spaces from the main lesion (at least 5 cells in each cluster) were defined as focal STAS, otherwise, it was diffuse STAS. Based on the aforementioned studies on lung ADC, in the same year, the World Health Organization (WHO) officially identified STAS as the fourth type of invasion of lung ADC (8), in addition to the other three types of invasions (non-lepidic growth, stromal infiltration, vascular and pleural infiltration). In addition, some studies had found that STAS was not only present in lung ADC (9-12). In 2017, Lu *et al.* (9) retrospectively analyzed 445 cases of stage I-III lung squamous cell carcinoma (SCC) and found that STAS was present in one-third of them. With more advanced clinical staging, the frequency of the appearance of STAS increased. Subsequent studies (10-12) have shown that STAS is also present in small cell lung carcinoma (SCLC), lung pleomorphic carcinoma (PC), and lung neuroendocrine tumors (NETs). Therefore, an objective definition of STAS can improve the understanding of the correlation between STAS and clinical prognosis.

Clinical significance

Since 1960, lobectomy has been the standard surgical treatment method for stage I non-small cell lung carcinoma (NSCLC) (13). In 2006, Okada *et al.* (14) conducted a multicenter trial and found that for patients with a peripheral cT1N0M0 non-small cell lung cancer of 2 cm or less, the 5-year disease-free survival (DFS) rate and OS rate for patients after sublobar resection were similar to those who underwent lobar resection, but the postoperative lung function of patients that underwent sublobar resection was significantly better. Therefore, sublobar resection should be considered as an alternative for stage IA non-small cell lung cancer 2 cm or less, even in low-risk patients. However, an increasing body of evidence suggests that for STAS-positive stage I lung ADC patients, sublobectomy yields a higher risk of recurrence than lobectomy, suggesting that STAS is associated with a poor prognosis in patients undergoing sublobectomy (15-17). Zhong *et al.* (18) found that the positive rates of STAS in lung ADC with solid nodules and subsolid nodules were 34.9% and 10.8%, ground glass opacity (GGO) components in the subsolid nodules with positive STAS were independently associated with good prognosis of patients. Kadota *et al.* (2) showed that STAS and surgical margins less than 1.0 cm from the tumor edge were important risk factors for local recurrence after sublobectomy of early lung cancer, when the resection margin was greater than 2.0 cm from the tumor edge, the STAS status was not correlated with local tumor recurrence, therefore, it is recommended that when sublobectomy is performed for patients with early lung cancer, a wider surgical margin should be set if STAS is involved. Chen *et al.* (19) showed that for patients with stage IA lung ADC who underwent sublobectomy combined with STAS positivity and patients with stage IB lung ADC combined with STAS positivity, adjuvant chemotherapy could achieve a better prognosis. In addition, some scholars have found that STAS is associated with poor prognosis of other types of lung cancer. Yanagawa *et al.* (20) retrospectively analyzed the clinicopathological data of 220 patients with lung SCC and found that for patients with stage I lung SCC, the 5-year RFS and OS rates of STAS-positive patients were significantly lower than STAS-negative patients, in patients with stage II and III lung SCC, STAS is not associated with recurrence or survival rate. Toyokawa *et al.* (10) analyzed the data of 30 patients with lung SCLC and found that patients with lung SCLC were prone to STAS, with a positive rate of 83%. Yokoyama *et al.* (11) studied the clinical and pathological data of 35 patients with lung PC and found that the RFS and OS of STAS-positive patients were significantly lower than STAS-negative patients, STAS was an independent risk factor for poor clinical prognosis by multivariate analysis. Aly *et al.* (12) studied the prognosis of 487 patients with pathological stage I-III lung NETs and found that STAS was related to an earlier occurrence of distant metastasis and a higher incidence of lung cancer-specific death. In summary, STAS positivity affects RFS and OS rates in lung cancer patients. Therefore, accurate prediction of STAS for lung cancer in the preoperative period is of great significance for selecting the optimal surgical approach (lobectomy or sublobectomy) and postoperative adjuvant therapy.

Computed tomography (CT) signs

Interestingly, a number of studies have indicated that some CT morphological characteristics of lung cancer are correlated with STAS. A retrospective study by Kim *et al.* (21) reported that STAS was more common in lung ADC with solid nodules, and the consolidation tumor ratio (CTR) was an independent predictor of STAS, with a threshold of 90%, the sensitivity of predicting STAS positivity was 89.2%, and the specificity was 60.3%. de Margerie-Mellon *et al.* (22) studied subsolid nodules and found that the overall size of the lesion, the size of the solid component, and the percentage of the solid component were positively correlated with STAS positivity. Toyokawa *et al.* (23) found that a positive pleural notch sign and negative ground-glass opacities were positively correlated with STAS positivity. Li *et al.* (24) studied 578 patients with lung ADC and constructed a multivariate logistic regression prediction model that included age, the maximum diameter, and the solid component ratio, with an area under the curve (AUC) value of 0.801 for predicting STAS. Qi *et al.* (25) found that CTR, ground glass ribbon, pleural connection, and absence of cystic airspaces were independent predictors of STAS, and the AUC value of STAS predicted by CTR was 0.760. Given that the evaluation of CT signs mostly relies on radiologists' experience, there is a certain degree of subjectivity, and different inclusion and exclusion criteria may lead to different conclusions (26). Therefore, the value of predicting STAS status using CT may be limited, and the results would need further verification.

18-fluorine-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT)

It is well-established that ^{18}F-FDG PET/CT can provide information on tumor morphology and the anatomical relationship with the adjacent structures and reflecting the metabolic activity of the tumor, and thus suggesting the tumor invasiveness (27). Suh *et al.* (28) did a study on 387 patients with NSCLC 2 cm or less. By combining preoperative imaging information and intraoperative frozen pathological results, a decision-making flowchart for predicting STAS was constructed, including the percentage of GGO on CT, the ratio of tumor/liver standard uptake values on ^{18}F-FDG PET/CT, the intraoperative histopathology of lepidic predominance, yielding positive sensitivity, specificity, and negative predictive values of 79.3%, 68.5% and 89.5%, respectively. Wang *et al.* (29) retrospectively analyzed the preoperative ^{18}F-FDG PET/CT-related data of 127 patients with early-stage lung ADC, including SUVmax, SUVmean, SUVpeak, metabolic tumor volume (MTV), and total lesion glycolysis (TLG), diameter and computed tomography volume (CTV), STAS risk prediction model developed by multivariate logistic regression analysis showed that SUV and TLG were valuable indicators for predicting STAS, the specificity and accuracy of the prediction model were 88.6% and 71.1%, respectively. Nishimori *et al.* (30) retrospectively analyzed the preoperative ^{18}F-FDG PET/CT-related parameters of 52 patients (55 lesions) to predict the STAS status of clinical stage I lung ADC, the results showed a significant variation in SUVmax between STAS-positive and STAS-negative groups, while there was no significant difference in MTV and TLG, receiver operating characteristic (ROC) curve analysis showed that when the SUVmax threshold was set to 2.48, the SUVmax prediction sensitivity was 89.5%, the specificity was 52.8%, and the AUC value was 0.74. Current studies have shown that SUVmax is an important indicator for predicting STAS. However, it should be noted that these studies were mostly retrospective, highlighting the possibility of bias during case inclusion, and these study results were not validated. Accordingly, the potential of ^{18}F-FDG PET/CT in predicting STAS and evaluating the prognosis of patients requires further studies.

Radiomics

Based on the analysis of CT and MRI images, radiomics extracts internal quantitative features and converts them into data for further mining in order to obtain the hidden biological values from the data (31). Over the years, some scholars have attempted to use radiomics to study STAS. Chen *et al.* (32) performed image segmentation and delineation on the lesions of 233 patients with stage I lung ADC and extracted important radiomics features to construct a model to predict STAS status, the AUC values of the internal and the external validation models were 0.63 and 0.69, respectively, indicating that CT-based radiomics has a definite value in the preoperative prediction of STAS in stage I lung ADC. Jiang *et al.* (33) performed univariate logistic regression analysis to screen the radiomics characteristics associated with STAS in 462 lung ADC patients and constructed a radiomics-based random forest (RF) machine learning model to predict STAS status, the 12 radiomics characteristics and patient age were found to be significantly correlated with STAS, and the RF model yielded an AUC value of 0.754 for predicting STAS. Zhuo *et al.* (34) performed radiomics feature extraction on 212 cases of tumor lesion area and peritumoral area (5, 10, 15 mm), combined with clinical features and made use of multivariate logistic regression to establish a radiomics nomogram to predict STAS, the maximum diameter of the solid component and mediastinal lymph node enlargement were identified as independent predictors of STAS, the AUC value of the training and validation sets were 0.98 and 0.99, respectively. Qi *et al.* (35) conducted a retrospective study of 216 lung ADC patients, based on the morphological signs of the lesion and the intratumoral and peritumoral radiomics characteristics, the ability of the single model and the comprehensive model to predict the STAS of lung ADC was compared, the AUC values of the comprehensive model training set, internal validation set and external validation set were 0.907, 0.897 and 0.909, respectively, which were significantly higher than those of the single model. Indeed, prediction models based on radiomics require strict procedures, including detection, segmentation, feature extraction and selection, and the operation process is complex and time-consuming (36). The clinical utility of CT-based radiomics in predicting STAS needs to be further investigated.

Deep learning (DL)

DL, also known as deep neural network learning, has shown great prospects in predicting the invasiveness of lung ADC by constructing multi-hierarchical nonlinear processing units to perform multi-level feature learning and improve the accuracy of disease diagnosis (37). Tao *et al.* (38) performed lesion segmentation and delineation on 203 cases of NSCLC patients with preoperative enhanced thin-slice CT, extracted radiomics features, and constructed a clinicopathological/CT model, a conventional radiomics model, a computer vision model, three-dimensional (3D) convolutional neural network (CNN) model and a combination model composed of 3D CNN model and clinicopathological/CT model to predict STAS status of NSCLC, the results showed that the 3D CNN model yielded superior performance than other models, with AUC values of 0.93 and 0.80 in the training and validation sets. At present, only one study has been conducted on the prediction of lung cancer STAS based on DL, and it is widely thought that its prediction efficiency has great room for improvement. In the future, better neural network models have to be constructed for improving the prediction efficiency.

Conclusions

STAS is a key invasion type of lung cancer, not only found in lung ADC but also in lung SCC, lung SCLC, lung PC, and lung NETs. For patients with early STAS-positive lung cancer, lobectomy is shown to have positive impact on patient prognosis. Although the gold standard for STAS detection and diagnosis is based on histopathological approach, preoperative CT and ^{18}F-FDG PET/CT have certain values in predicting the status of STAS, thus assist clinicians to select the optimal surgical approach and postsurgical treatment. Meanwhile, the prediction of STAS based on radiomics and DL represents a future research direction. At present, the mechanism of STAS remains controversial. Little is currently known about whether STAS is a key invasive pattern of lung cancer, or whether STAS can be used as a reference indicator in TNM staging of lung cancer, highlighting the need for further research. Most of the previous studies were based on retrospective analysis, and their findings were not externally validated. Accordingly, their clinical practicability needs to be further explored.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2593/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2593/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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