Lung Cancer 146 (2020) 127–133

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

The role of spread through air spaces (STAS) in lung adenocarcinoma prognosis and therapeutic decision making

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ARTICLE INFO

Keywords:
NSCLC
Lung cancer
STAS
Adenocarcinoma

ABSTRACT

Spread through air spaces (STAS) was included as a novel pattern of invasion in lung adenocarcinoma by the World Health Organization in 2015. Since then, multiple studies have investigated the association of STAS with clinicopathological and molecular features and its implication in the prognosis of early stage lung cancer patients undergoing different surgery types. The aim of this comprehensive review is to present current data on the role of STAS and its perspective in lung adenocarcinoma management.

1. Introduction

Lung cancer is the most common malignancy with the highest mortality worldwide [1]. Until recently, the patterns of cancer progression were via vascular, lymphatic, or transcoelomic spread. In 2015, the World Health Organization (WHO) classification of lung cancer included the concept of Spread through air spaces (STAS) as a new pattern of invasion in lung adenocarcinoma (ADC) [2]. Since then, STAS has been described in multiple histologic types apart from ADC and it has been the subject of extensive research regarding its value in therapeutic decision making.

2. STAS as an invasion pattern in lung cancer

In the WHO classification, STAS is defined as 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. Although the term aerogenous spread was used long before STAS, its role was unclear. In 2002, micropapillary component, already described in ovarian, breast and urinary bladder cancer, was also reported in lung ADC, as a histological component likely to metastasize and carry an unfavorable prognosis [3]. After its clinical value was becoming clearer, in the 2011 classification of ADC by International Association for the Study of Lung Cancer (IASLC), American Thoracic Society and European Respiratory Society, micropapillary pattern was recognized as one of the 5 major growth patterns (lepidic, papillary, acinar, micropapillary and solid) and was included as a new histologic subtype with poor prognosis [4]. Onozato et al. [5,6] used the term “tumor island” for isolated, large collections of tumor cells within alveolar spaces without well-demarcated micropapillary configuration. In this study although the authors observed that tumor islands were still interconnected with each other and with the main tumor by 3D-reconstruction, the prognosis was worse in ADC with this pathologic finding.

The concept of STAS and its prognostic value was first validated by Kodota et al. [7] in a retrospective cohort of 411 small (< 2 cm) resected stage I ADC. STAS was significantly correlated to distant and locoregional recurrence in the limited resection group, while there was no association with recurrence in the lobectomy group. In multivariate analysis, the presence of tumor STAS was an independent and the only risk factor of any recurrence in the limited resection group (HR: 3.08, $p = 0.014$). In a study presented in the same year by Warth et al. [8], STAS was again associated with significantly reduced overall survival (OS) ($p = 0.02$) and disease-free survival (DFS) ($p = 0.004$), although in the multivariate analysis its unfavourable prognostic value was stage dependent. Notably, only a minority of the included patients underwent limited resection (1.9 % wedge resection and 1.2 % segmentectomy), and therefore subgroup analysis comparing recurrence rates was not

Abbreviations: STAS, Spread through air spaces; WHO, World Health Organization; ADC, Adenocarcinoma; IASLC, International Association for the Study of Lung Cancer; HR, Hazard Ratio; OS, Overall Survival; DFS, Disease-free survival; NSCLC, Non-Small Cell Lung Cancer; GGO, Ground-glass opacity; RFS, Recurrence-free survival; EGFR, Epidermal Growth Factor Receptor; ALK, Anaplastic lymphoma kinase; MTA1, Metastasis-associated protein 1; MUC21, Mucin-21; CT, Computed tomography; STAKS, Spread Through A Knife Surface

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https://doi.org/10.1016/j.lungcan.2020.04.026
Received 16 January 2020; Received in revised form 20 April 2020; Accepted 22 April 2020

performed.

Those two studies set the groundwork to establish criteria to distinguish STAS from artifacts. Warth et al. [8] scored tumor cells as STAS when there was no direct connection of the cells to the main tumor mass, they were arranged in loose small groups, and the distribution was consistent with the overall configuration of the circumferential tumor edge, while according to Kadota et al. [7], tumor floaters could be identified by the presence of clusters of cells randomly scattered over tissue and at the edges of the tissue section. Jagged edges of tumor cell clusters or linear strips suggested tumor fragmentation. Tumor cells distant from the main tumor were 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. Kadota's criteria for STAS diagnosis were recently shown to be highly reproducible in a study [9] of selected images assessed by 10 observers from 5 institutions, reporting a unanimous agreement in 24/30 (80 %) cases and an average kappa value of 0.857 (range 0.614–1.00). However, reproducibility of these criteria has yet to be assessed on glass slides in larger studies.

3. STAS association with clinical characteristics

STAS incidence ranges from 14.8 to 60.5% in Non-Small Cell Lung Cancer (NSCLC) ADC [7,8,10–20]. This frequency discordance can be attributed to pre-analytical variables and interpretation by pathologists. STAS classification also differs among studies, by the use of the distance from main tumor, the number of intervening alveoli or morphological features. The distance between ADC tumor surface and STAS is reported between 0.2 and 8.5 mm measured by ruler and 1–58 alveolar spaces [7,14]. Warth et al. [8] categorized STAS according to its distance from the primary lesion as limited if solid cell nests were no more than 3 alveoli away from primary tumor and extensive if it was more than 3 alveoli away. In other studies [11,13], STAS was categorized as low (1–4 single cells or clusters) and high (> 5 single cells or cell clusters) with the prognostic value of STAS being correlated with the grade while, Lee et al. [15] used morphology to classify tumor STAS into four patterns.

STAS is related to specific growth patterns of ADC and is found in invasive histologic patterns, while its presence is an exclusion criterion for ADC in situ and minimally invasive ADC [2,14,21]. Early studies [7,8] showed that STAS was rare in lepidic-predominant ADC, while there was a strong correlation with high-grade histological patterns. Similarly, in subsequent studies [15,22,23] STAS was associated with the absence of lepidic component and the presence of micropapillary, solid and cribriform predominant types, although cribriform is not an official subtype of the WHO classification [2]. The association of STAS with cribriform component was further supported by a study by Ding et al. [24] in which 71.6 % of tumors with a cribriform component were STAS positive.

STAS is generally associated with aggressive tumor characteristics like high tumor stage, nodal-positivity with distant metastasis, lymphovascular and pleural invasion, males, smoking history and higher carcinoembryonic antigen value [7,8,10,11,14,15,17–20,22], while there is no correlation between STAS and age or surgery type [25]. However, some studies11,15] have not confirmed an association of sex and smoking status with STAS. Current studies that are focusing on STAS correlations with clinicopathological features in lung ADC are shown in Table 1.

4. Prognostic significance of STAS in lung ADC

Surgical resection in patients with early-stage NSCLC, provides high cure rates, although the 5-year post-operative DFS is only 55.1 % in pathological stage I patients [26]. Although lobectomy is the preferred procedure over limited resection for early stage NSCLC with a proven benefit [27], the use of sublobar resection is still considered for small, non-invasive or minimally invasive lesions, especially those with ground-glass opacity (GGO) characteristics [28] and is increasing [29] although no definitive criteria exist to select candidates for limited resection. Based on current knowledge, the shorter survival could be explained by the presence of STAS.

As it was becoming clear that STAS may be a crucial risk factor of recurrence in stage I ADC treated with limited resection, more studies focused on its prognostic value in different surgery types. Dai et al. [14] found that STAS was an independent prognostic factor for poor recurrence free survival (RFS) (HR = 1.66, p = 0.043) and OS (HR = 2.10, p = 0.009) and that patients with stage IA ADC and STAS positivity had a similar prognosis to those with stage IB ADC. Subgroup analysis showed that tumor STAS affected survival in ADCs larger than 2–3 cm, while among patients with ADCs < 2 cm, STAS failed to significantly stratify the prognosis. In this study, although 95 % of patients underwent lobectomy, the prognostic impact of STAS was still evident. As adjuvant chemotherapy has been proven to benefit stage IB lung ADC with solid/micropapillary patterns [30], this finding raises the question whether STAS should be considered a staging factor similar to pleural invasion.

Shiono et al. [31] reported that patients with STAS undergoing sublobar resection had a higher rate of pulmonary metastases than patients with STAS that underwent a lobectomy (25.8 % vs 8.2 %). STAS was a significantly worse prognostic factor for the sublobar resection group but not the lobectomy group. Another study [32] showed that the risk of local recurrence in limited resection was significantly associated with STAS (HR: 12.24, p = 0.001) and tumor margins less than 1 cm (HR: 6.36, p = 0.02). Interestingly, in patients with a resection margin greater than 2 cm, no local recurrence was observed regardless of the surgical operation or the presence of tumor STAS. To take a step further, Eguchi et al. [33] investigated 1497 T1 patients who underwent lobectomy or sublobar invasion and found that sublobar resection was significantly associated with recurrence (HR = 2.84, p < 0.001) and lung cancer-specific death (HR = 2.63 p = 0.021) in patients with STAS but not in those without STAS. Additionally, patients with STAS who underwent sublobar resection had a higher risk of locoregional recurrence regardless of margin-to-tumor ratio, while in patients without STAS locoregional recurrence was associated only with margin-to-tumor ratio less than 1. Similar results were demonstrated in an independent cohort by Kadota et al. [34].

An important finding reported by Eguchi et al. [33] was that pathologists were able to recognize STAS on intraoperative frozen sections with high sensitivity and specificity (71 % and 92 %, respectively). In previous reports, evaluation of STAS in frozen sections had unacceptably low sensitivity. In an early study [35], even the micropapillary pattern detection was suboptimal. Similarly, STAS evaluation in frozen sections from resected lung ADC had low sensitivity (50 %) and negative predictive value (8%), as reported by Walts et al. [36].

Three recent meta-analyses further support STAS as a negative predictor of response and recurrence. Chen et al. [37] pooled data from 3754 patients from 14 studies and found that STAS was associated with inferior RFS (HR: 2.288) and OS (HR: 1.958) in lung ADC subgroup analysis. Similarly in a meta-analysis by Wang et al. [25], STAS was an independent negative prognostic factor for progression free survival (PFS) (HR: 1.724) and OS (HR: 1.612), while Liu et al. [38] included 12 studies with a total of 3564 patients of all histologic subtypes and showed that the presence of STAS predicted a worse outcome for 5-year RFS (HR: 1.84) and OS (HR: 1.78). Importantly, while in the lobectomy group there was a non-statistically significant trend towards shorter RFS in patients with STAS compared to patients without STAS, in the limited resection group STAS was a significant risk factor for recurrence (HR: 4.05). Other studies [10,11,13,15,39] have also validated the invasive pattern of STAS as a significant prognostic marker in resected early stage NSCLC. In a study by Liu et al. [40], the authors built a prognostic model for invasive lung ADC including STAS, visceral pleural invasion, vascular invasion and histological subtype, which

Table 1
STAS frequency and factors associated with STAS in lung ADC.

Study	Year	Study population	Histologic type	% STAS	Clinicopathological factors	Histology	Mutations	Prognosis	Imaging features
Onozato et al [5]	2013	261	ADC	22.2 (Tumor Islands)	Smoking, high nuclear grade	Solid or micropapillary pattern	KRAS (+)	↓RFS	NR
Kadota et al [7]	2015	411	ADC	38	Lymphovascular invasion	Micropapillary and solid component	NR	↑RR in limited resection group	NR
Warth et al [8]	2015	569	ADC	50.6	Male, pathological stage, nodal positivity, distant metastasis	Invasive pattern	EGFR (-) BRAF (+) No association with KRAS	↓OS, ↓DFS (stage dependent)	NR
Shiono et al [10]	2016	318	ADC	14.8	Lymphovascular and pleural invasion, male, smoking, stage IB, CEA	NR	EGFR (-)	↓OS, ↓RFS	Solid nodule, SUVmax
Dai et al [14]	2017	544	ADC	30.3	Male	Invasive pattern	NR	↓OS, ↓RFS, IA with 2−3 cm and STAS (+) similar prognosis to IB	NR
Uruga et al [13]	2017	208	ADC	47.6	Lymphovascular and pleural inasion, tumor size > 10mm	Solid predominant component	NR	↓RFS	NR
Lee et al [15]	2017	316	ADC	50.6	Lymphovascular invation, pathological stage, nodal positivity	Invasive pattern	EGFR (-), ALK (+), ROS1 (+), No association to KRAS	↑RR, ↓RFS	NR
Masai et al [32]	2017	508	All	15	Lymphovascular and pleural invasion, male, smoking	Micropapillary and solid component	NR	↑RR	NR
Toyokawa et al [11]	2018	276	ADC	55.4	Pleural invasion, tumor size, CEA	Invasive pattern	No association to EGFR mutations	↓OS, ↓RFS	Tumor diameter, SUVmax, C/T ratio
Eguchi et al [33]	2018	1497	ADC	NR	NR	NR	NR	↑RR, ↓LCSD, ↓RFS (limited resection vs lobectomy)	NR
Toyokawa et al [16]	2018	327	ADC	58.4	Tumor size, nodal positivity, pathological stage	NR	NR	NR	Presence of notch, absence of GGO, C/T ratio
Kim et al [22]	2018	276	ADC	33.3	Lymphatic invasion, nodal positivity	Papillary, micropapillary, solid, and cribriform component	EGFR (-), ALK (+)	NR	Solid nodule, tumor density, C/T ratio, central low attenuation, ill-defined opacity, no air bronchogram, % of solid component
Song et al [23]	2019	277	ADC	31	Lymphovascular and pleural invasion	Micropapillary and solid component	NR	NR	Solid nodule
Ding et al [24]	2019	208	ADC	51.4	Tumor size, nodal positivity	Micropapillary, solid and cribriform component	NR	↓OS, ↓RFS	NR
Kadota et al [34]	2019	735	ADC	34	Lymphovascular invasion, male, nodal positivity, pathological stage	Micropapillary, solid and cribriform component	ALK (+)	↓OS, ↓RFS (limited resection vs lobectomy)	NR
Terada et al [17]	2019	76	ADC	60.5	Lymphatic invasion, absence of skip N2 metastases	Micropapillary and papillary component	NR	↓RFS (Univariate analysis, stage III N2)	NR
Ren et al [18]	2019	752	ADC	29.9	Male (lobectomy), T pathological stage (sublobar resection)	Micropapillary and solid component	NR	↓OS, ↓RFS (Sublobar resection)	NR
Shiono et al [19]	2019	848	All	16.4	Lymphovascular and pleural invasion, male, smoking, CEA, tumor size	NR	NR	↓RFS	NR
Kim et al [20]	2019	193	Acinar/papillary-predominant ADC	48.7	Lymphovascular invasion, pathological stage	Micropapillary and solid pattern, absence of lepidic pattern (second most predominant)	EGFR (-), ALK (+)	↓RFS, ↓OS (Univariate analysis)	NR

could effectively predict recurrence and mortality.

STAS is an important pathological finding that in the future could even be considered as a factor in the staging system to guide therapeutic decisions. In clinical practice, if STAS can be accurately identified in frozen sections from limited resections, a more extensive surgical approach or meticulous radiological follow-up could be considered. To this direction, an intraoperative specimen containing tumor and normal lung parenchyma could be acquired for review. Whether adjuvant treatment would benefit patients with stage IA tumors found positive for STAS is still unknown as prospective randomized trials are needed. Before this happens though, a universal pathological protocol about STAS evaluation is warranted.

5. STAS in histologic subtypes other than ADC

STAS was initially described in lung ADC but recent studies have identified this novel invasion pattern in lung squamous cell carcinoma (SCC), pleomorphic carcinoma and neuroendocrine tumors (NETs) including small-cell lung cancer (SCLC).

For several years pathological staging was the only proven poor prognostic factor in invasive SCCs, while STAS was only recently recognized to have a prognostic value. In a study [12] including 216 SCC tumors, STAS was an independent predictor of RFS (HR = 1.61, p = 0.023) in patients undergoing resection and was associated with increased risk of locoregional and distant metastasis. The incidence of STAS was 40 %, most commonly found in cases with lymph node metastases (p = 0.037), higher pathologic stage (p = 0.026), and lymphatic invasion (p = 0.033). Interestingly, STAS was also associated with high-grade tumor budding (p = 0.006), defined as the presence of isolated small tumor nests (< 5 tumor cells) in the stroma of the invasive tumor edge, a finding associated with poor prognosis in SCC [41].Another study by Lu et al. [42] identified STAS in 30 % of resected stage I to III lung SCC tumors. Subgroup analysis showed that STAS was associated with higher rates of recurrence (HR: 1.5, p = 0.034) and cancer-specific death (HR: 1.75, p = 0.016) in the lobectomy group, while in patients undergoing limited resection, there was a trend toward worse RFS that did not reach statistical significance. STAS was again more frequently found in cases with high-grade morphologic pattern, aggressive tumor behavior and high Ki-67 labeling index. While in ADC, STAS is composed of micropapillary pattern, solid nests or single cells, in SCC studies all STAS lesions have a solid nest pattern [12,42]. A lower STAS incidence (19.1 %) has been reported by Yanagawa et al. [43]. In this study, STAS was again an independent prognostic factor of worse RFS (HR: 3.27, p = 0.0004) and OS (HR: 1.54, p = 0.0013) in stage I tumors, but not in stage II and III. Therefore, the presence of STAS may be a promising prognostic marker in SCC but more studies are warranted to elucidate its clinical value and application.

STAS has been identified in lung neuroendocrine tumors (NETs) too, although its role remains unclear. In a study by Toyokawa et al. [44] STAS positivity was found in 83 % of SCLC cases (25/30 patients) but was not associated with any clinicopathological characteristics or prognosis. Similarly high STAS incidence was reported by Altinay et al. [45], as STAS was identified in 20.5 % of typical carcinoids (TCs), 48 % of atypical carcinoid (ACs), and 76.7 % of high-grade carcinomas (large cell neuroendocrine carcinoma (LCNEC) and SCLC), although the number of patients in this group was small. In carcinoid tumors, the presence of STAS retained a statistically significant association with adverse prognosis. Conversely, Aly et al. [46] reported that STAS was identified in 26 % of NETs (16 % of TCs, 37 % of ACs, 43 % of LCNEC, and 46 % of SCLCs) and was associated with higher cumulative incidence of recurrence (CIR) (HR = 2.85, p < 0.001) and lung cancer–specific cumulative incidence of death (LC-CID) (HR: 2.72, p < 0.001), independently of tumor stage. STAS was also associated with a threefold higher risk of brain metastasis and higher distant recurrence. In these studies [45,46] STAS was associated with age, smoking history, adjuvant therapy, lymph node metastasis, higher tumor stage, lymphovascular and pleural invasion, necrosis, high mitotic count and high Ki-67 index.

Lung pleomorphic carcinoma is a rare subset of sarcomatoid carcinoma characterized by poor survival [2,47]. In resected pleomorphic carcinoma [48], STAS was found in 40 % of cases (14/35 patients) as single cells, small tumor cell clusters, or tumor nests. STAS was associated with tumor necrosis, a known negative predictor of outcome [49] and was an independent prognostic factor for short RFS (HR: 4.76, p = 0.014) and OS (HR: 12.209, p = 0.042). However, all patients in this study underwent lobectomy or bilobectomy.

6. Molecular alterations related to STAS

In terms of molecular alterations, reports have been conflicting. Several studies [8,10,15,50] have found that STAS positivity is associated with wild type EGFR and the presence of BRAF mutations, while others showed no association to EGFR [11] or KRAS status [8,15]. STAS has also been found to be more common in tumors with ROS1 and ALK rearrangements [15,22,51].

So far there are no studies on the characterization of tumor microenvironment immune cell populations and their role in STAS pathogenesis. Neutrophils [52] might play a role in tumor shedding and aerogenous spread mainly through cell-to-cell contact rather than through soluble mediators. Regarding immune checkpoint expression, one study found no correlation between PD-L1 and STAS prevelance [11].

The protein and signaling pathways responsible for STAS have not been elucidated yet. While STAS in SCC is associated with high mitotic rate and Ki-67 expression [42], no difference in proliferative activity in ADC has been found [8]. A positive association between metastasis-associated protein 1 (MTA1) and STAS in stage I to III resected NSCLC ADC has also been described [53]. MTA1 is often overexpressed in the tumor microenvironment and has been associated with high metastatic rate and poor prognosis [54]. Another study that included tumors with ROS rearrangement showed frequent aerogenous spread with loss of E-cadherin [51]. Before the inclusion of STAS as an invasion pattern, a study [55] investigated the role of major regulating molecules for cell attachment and found a correlation between laminin-5 and aerogenous spread as well as ligand independent activation of EGFR pathway, probably conferring anoikis resistance. Aerogenous spread has also been correlated to ultrastructural changes of alveolar capillaries' endothelial cells, like active proliferation and regeneration [56]. Tumor microenvironment interactions might also play a role in STAS through dysfunction of cell adhesions [57]. In one case of lung ADC [58] consisting almost entirely of single cancer cell STAS, there was a high expression of mucin-21 (MUC21) by mRNA sequencing and immunohistochemistry (IHC). This was further confirmed by IHC analysis in an unselected series of 120 lung ADCs in which strong membranous expression of MUC21 correlated with incohesiveness.

7. STAS and preoperative imaging

STAS is a microscopic finding that implies a post-excision diagnosis by definition. As the presence of STAS in pathological specimens is a negative prognostic factor in early NSCLC treated with limited resection, pre-surgical stratification for STAS risk by radiological features could guide therapeutic decisions.

Although it was only recently recognized as an invasion mechanism, radiologists were active to investigate whether STAS positivity could be predicted by imaging criteria. A recent study even proposed a definition [59] based on computed tomography (CT) radiological features as: intrapulmonary discontinuous spread of neoplastic cells through airspaces and airways with discontinuous foci seen close to the primary tumor as satellite foci at distance including in the contralateral lung. Recent studies show that CT images may help identify the presence of

STAS in lung ADC. CT features that suggest STAS are centrilobular nodules and branching opacities (tree-in-bud nodules) with poorly-defined margins and ground glass attenuation [59]. STAS is also associated with spiculation, absence of air bronchogram, pleural retraction, and presence of notch [16,22]. Tumor diameter on CT, and specifically tumor diameter larger than 2 cm, has also been reported to be predictive of STAS [11,16,60]. Other studies show that the solid component of nodules [10,11,22] is associated with positive STAS. Interestingly, Kim et al22] reported that the percentage of solid component (defined as maximum diameter of the solid component/maximum diameter) of the lesion on CT but not tumor diameter was an independent predictor of STAS and a cut-off value of 90 % had a high sensitivity and specificity (89.2 % and 60.3 % respectively).

A recent retrospective study [61] of 62 patients showed that STAS was mainly found in lesions appearing solid by CT and was associated with higher CT value in Hounsfield units ($p = 0.011$) but it was also present in 1/13 cases of GGO. Another study [11] also reported STAS positivity in 10/36 cases of pure GGO by CT features, suggesting that GGO on imaging does not preclude presence of invasive patterns like STAS. Similarly, STAS positivity was significantly related to solid nodule on CT in a series of resected stage I ADC by thoracoscopic surgery [23]. In primary tumors evaluated by PET-CT higher maximum standardized uptake value has been associated with STAT presence [10,11].

Even though pre-surgical risk stratification by STAS is a promising approach, there are inherent limitations. CT technical parameters, like CT scan section thickness or the use of enhanced scans can affect accurate characterization of nodules. Additionally, intra- and inter-reader variability affects reproducibility. As technology advances, the application of computer aided diagnostic approaches like deep learning (radiomics) of both nodular and peri-nodular features could be useful in identifying STAS radiological characteristics not perceived by human reader.

8. STAS as an artifact

There is still a lot of skepticism about the inclusion of STAS as an invasion pattern, arguing that it is not sufficiently studied or mature to be included into the WHO classification, despite the abundance of good quality data coming from multiple institutions worldwide supporting its clinical relevance.

STAS has been criticized to be an artifact caused by disruption of tumor cells and spread along the alveolar spaces ex vivo attributed to lung specimen sectioning, a phenomenon known as “Spread Through A Knife Surface” [62] (STAKS) and mechanical forces. Extraneous tissue contamination in pathological specimens has been described as a potential cause of diagnostic error, especially if the misplaced fragments are from malignant tissue. This artifact may arise during tissue processing and slide preparation and its frequency ranges from 0.01 % to 2.9 % [63,64]. A STAS like phenomenon was recently described in three cases of diffuse idiopathic pulmonary neuroendocrine (NE) cell hyperplasia [65], in which freely-floating aggregates of hyperplastic NE cells were spilling over into air cavities and seen to emanate around foci of NE hyperplasia. The authors supported that displacement of NE cell-unaccompanied bronchial epithelium sheets and occurrence of erythrocytes in air spaces in close relationship with NE cells fragments point towards an artifactual origin upon mechanical fragmentation of lung tissue. However, in this study the authors did not use the previously defined criteria for STAS diagnosis, which distinguish STAS from artifacts. Furthermore, as pulmonary neuroendocrine cell proliferations (tumorlets) often extend beyond the basement membrane into the peribronchial tissue forming cell nests, it is unclear whether the detached cells described by the authors are indeed an artifact or could be interconnected to the tumorlets.

A prior prospective study by Blaauwgeers et al. [66] showed that tumor islands or loose tumor cells were identified in 73 % of cases (higher than the reported STAS incidence) and the majority could be attributed to mechanical artifacts related to surgical resection and gross room specimen processing. Benign loose fragments within alveolar spaces were also found in 61 % of the cases. Interestingly, although the authors support that STAS can be attributed to mechanical forces caused by specimen handling, they did not demonstrate a different incidence of loose fragments in different procedure groups (Video assisted thoracoscopic surgery vs thoracotomy) and some loose tissue fragments were found in areas on the slide that were cut before passing through tumor tissue. In a case series, Lu et al. [67] also described two cases of extensive STAS predominant pattern that the main tumor was not cut either by the surgeon or pathologist providing further evidence that STAS is not a STAKS artifact. Furthermore, Blaauwgeers et al. did not demonstrate how the already established criteria to distinguish STAS from artifacts were applied in their study. Additionally, there was a great variation in tissue sample size and normal parenchyma proportion across sections, while the lack of clinical follow up precluded the comparison of the prognostic value associated with STAS compared to tumor floaters. Taken together, the findings of this study should be interpreted cautiously.

Other hypotheses for STAS origin are poor or delayed tissue fixation and although exceedingly rare, tumor seeding after biopsy as it increases the risk of tumor cell dissemination [68,69]. Shiono et al. [10] in their study could not find differences in the rates of STAS between surgical procedures, between the patients who underwent initial lobectomy or segmentectomy, or those who underwent other procedures like biopsy. Similarly, several other studies did not find significant differences in STAS positivity among different surgical procedures (lobectomy vs limited resection) [7,14], although thoracotomy and thoracoscopic surgery were not evaluated separately. However, in a recent study [23] that included stage I ADC tumors resected by thoracoscopic surgery, the authors hypothesized that bigger specimen in lobectomy was more likely to present STAS than smaller specimen in sublobar resection. Although there was a higher incidence of STAS in the lobectomy group compared to the limited resection group, the difference was not statistically significant in multivariate analysis.

Another issue for debate is the mechanism of development and survival of the floating tumor cells that constitute the STAS entity. Currently, there is lack of biological understanding of how STAS occurs. STAS by definition requires cell discohesiveness, detachment from the surrounding extracellular matrix and anchorage-independent survival. Although detachment of normal epithelial cells form basement membrane causes apoptosis (anoikis) [70,71], anchorage-independent survival and growth especially of transformed cells has been previously described [72,73]. Specifically, micropapillary lung ADC loose cells show anchorage independent growth and resistance to apoptosis [74]. In a recent study [75], STAS cells were focally re-attached to the alveolar walls of the lung parenchyma in proximity to the alveolar wall vasculature with a lack of endothelial cells and CD31 expression, a finding consistent to a non-angiogenic pattern of lung cancer and explained by “co-option” of pre-existing blood vessels. Vascular co-option is a survival and growth mechanism of tumors cells beyond the tumor edge in which blood supply in obtained by hijacking the existing vasculature. The therapeutic implication of whether STAS presence, as a non angiogenic form of lung cancer, would predict resistance to anti-angiogenesis treatment like bevacizumab still needs to be investigated.

Although there is a prognostic argument in favor of STAS, there is also criticism that STAS is only correlated with adverse prognostic factors such as high-grade histologic patterns, lymphovascular and visceral pleural invasion. However, in a meta-analysis by Chen et al. [37] the prognostic value of STAS remained significant in multivariate analysis when high-grade histologic patterns of ADCs and other risk predictors were included. Given the consistency of the findings in multiple independent studies and different histologic types, it seems unlikely STAS is an artifact. The distinction though between an artifact and STAS has significant clinical importance regarding adequacy of resection and risk of local recurrence. Pathologists need to be rigorous

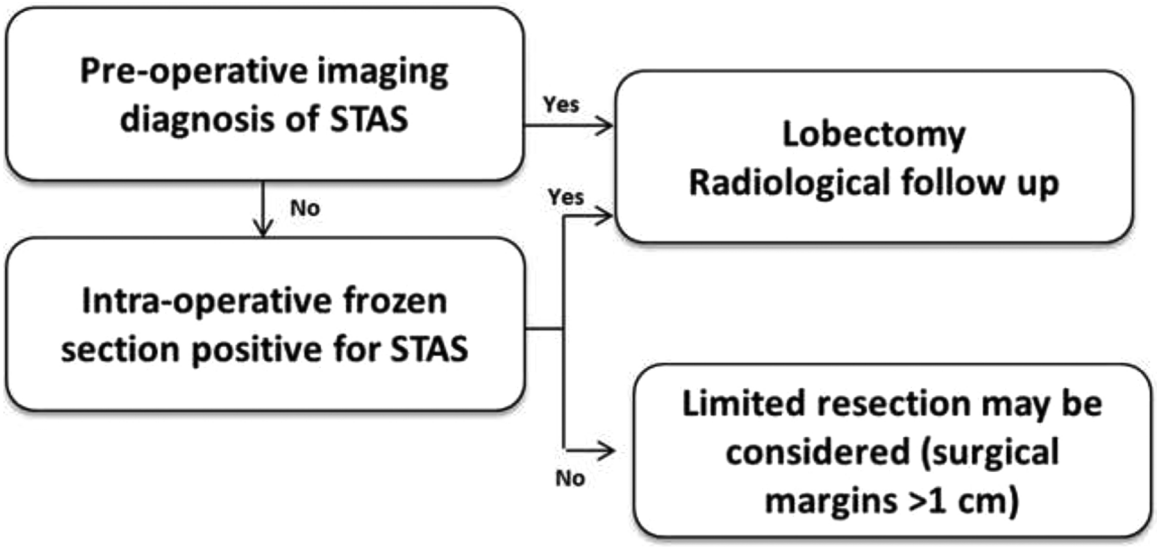

Fig. 1. Suggested therapeutic approach by STAS positivity in lung ADC tumors < 3 cm.
Abbreviations: STAS = Spread through air spaces.

with the use of standardized tissue handling protocols of surgical material in order to avoid creation of artifacts with floating tumor cells or clusters. On the other hand, surgeons would have to provide adequate normal lung parenchyma to pathologist for accurate STAS evaluation.

More studies are required to clarify whether STAS has a role in staging and clinical management. Additionally, the criteria used to define STAS vary among studies. Based on current data, preoperative diagnosis of STAS could guide the selection of surgical procedures. Patients with tumors < 3 cm should be examined for STAS to assess whether limited resection is a reasonable option, as it leads to higher risk of recurrence in patients with STAS. If the patient is eligible for limited resection, the surgeon needs to ensure sufficient surgical margins larger than 2 cm. A suggested therapeutic approach is presented in Fig. 1.

9. Conclusion

In summary, STAS has been already identified in multiple histologic subtypes of lung cancer and is suggested to represent a poor prognostic factor for recurrence and survival. Its role in staging and therapeutic decisions is still unclear, but identification of this histologic finding by pathologists provides useful prognostic information. More studies are warranted to uniform pathological protocols for STAS definition and classification, as there is great discordance among studies. It is also important to find ways to minimize inter-observer variation and increase reproducibility and diagnostic agreement among pathologists. As most reports are coming from retrospective studies, more prospective clinical trials are necessary to define postoperative strategy and optimal treatment approach.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

All authors have no conflict of interest to report.

Acknowledgement

None.

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