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Review / Derleme

Spread through air spaces positivity and extent of resection in patients with Stage I non-small cell lung cancer: A contemporary review

Evre I küçük hücreli dışı akciğer kanseri hastalarında hava yolları ile yayılım pozitifliği ve rezeksiyon genişliği: Güncel bir derleme

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ABSTRACT

The concept of spread through air spaces is a type of cancer spread that is unique to lung and may be established as a criterion for invasion. It is a potential risk factor for recurrence and poor prognosis in patients with early-stage non-small cell lung cancer. This review provides a contemporary overview on recent data in this field and aim to help surgeons to decide the extent of resection according to patients' spread through air spaces status.

Keywords: Early-stage lung cancer, resection, spread through air spaces.

ÖZ

Hava yolları ile yayılım kavramı, akciğerlere özgü bir kanser yayılım şekli olup invazyon kriteri olarak kabul edilebilir. Erken evre küçük hücreli dışı akciğer kanserinde nüks ve kötü prognoz için muhtemel bir risk faktörüdür. Bu derlemede bu alandaki güncel verilere ilişkin bir genel bakış sunuldu ve cerrahlara hastaların hava yolları ile yayılım durumuna göre cerrahi genişliği belirlemede yardımcı olmak amaçlandı.

Anahtar sözcükler: Erken evre akciğer kanseri, rezeksiyon, hava yolları ile yayılım.

Spread through air spaces (STAS) is a phenomenon of cancer spread which is unique to the lung. It was first described by Kadota et al.[1] in 2015 and has received considerable interest since then. Currently, lobectomy is considered the standard care for the management of early-stage non-small cell lung carcinoma (NSCLC). However, owing to the advancement of imaging techniques and recognition of the significance of low-dose thoracic computed tomography (CT) screening, small-sized NSCLC can be detected more frequently than before. Thus, despite ongoing concerns about its potential for local recurrence, sublobar resections (SRs) have been increasingly performed in patients with Stage I NSCLC.[2-6] Most recent studies have demonstrated that STAS is a potential risk factor for recurrence and poor prognosis in patients with early-stage NSCLC, particularly following SR.[5-8]

In this review, we summarize the current literature regarding STAS, investigate its impact on clinical outcomes in Stage I NSCLC, and aim to help surgeons to decide the extent of resection according to patients' STAS status.

Definition of STAS

According to the 2015 World Health Organization (WHO) Classification of Lung Tumors, STAS is defined as *"spread of micropapillary clusters, solid nests, and/or single cancer cells into airspaces in the lung parenchyma beyond the edge of the main tumor"* and may be established as a criterion for invasion, such as lymphovascular or pleural invasion.[9]

Histology of STAS

Although STAS was initially observed in adenocarcinomas, it essentially occurs in other

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histological types of lung cancer types, including squamous cell carcinoma (SCC), neuroendocrine tumors, and pleomorphic carcinoma. The reported incidence of STAS is quite variable ranging from 15 to 80%.[6] It is rarely observed in adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), or pure ground-glass (GG) tumors[6,10,11] with one exception study showing 29% STAS positivity in pure GG and 34% positivity among atypical adenomatous hyperplasia (AAH), AIS, and MIA tumors.[12] In most studies, STAS positivity is associated with micropapillary and/or solid patterns and less lepidic pattern with higher rates of Kirsten rat sarcoma viral oncogene *(KRAS)* or B-Raf *(BRAF)* mutations, anaplastic lymphoma kinase *(ALK)* or c-ros oncogene 1 *(ROS1)* rearrangements, and wild-type epidermal growth factor receptor *(EGFR)* in lung adenocarcinoma.[1,6,13-15]

Prognostic Implication of STAS

Recent studies on NSCLC have shown that STAS has been associated with worse long-term outcomes, particularly after SR.[5-7,16-18] Shiono et al.[18] investigated 514 clinical Stage IA NSCLC patients who underwent lobectomy or SR and found that patients who underwent SR with STAS positivity had worse survival, a higher incidence of locoregional recurrence, and pulmonary metastasis than those without STAS. The authors found no significant difference among the patients who underwent lobectomy. In their most recent study, the same authors evaluated 217 patients with clinical Stage IA NSCLC and compared the prognostic impact of STAS in patients who underwent wedge resection (WR) or segmentectomy.[6] They clearly demonstrated that STAS was a significant prognostic factor for patients with clinical Stage IA NSCLC who underwent WR, but not for those who underwent segmentectomy. They rationalized their result with the wider surgical margin achieved with segmentectomy, potentially preventing the spread of tumor cells. They also identified a cut-off solid tumor size of 1.7 cm on chest CT predicting the positivity of STAS and, based on these findings, they advocated segmentectomy or lobectomy as the reasonable approach, when the solid tumor size on CT was greater than 1.7 cm.

In another study, Jia et al.[15] examined the effect of STAS on clinicopathologic features, molecular characteristics, and prognosis in patients with both adenocarcinoma and SCC. They found that STAS was associated with significantly shorter disease-free survival (DFS) and overall survival (OS) in patients with adenocarcinoma. In SCC patients, STAS was associated with shorter OS, although it did not reach statistical significance. Besides, DFS was not affected by the STAS status in the SCC cohort. However, in both cohorts, particularly in adenocarcinoma patients, STAS positivity was significantly higher in tumors with an aggressive behavior and higher p-stages.

In a recent meta-analysis, Chen et al.[16] examined the prognostic impact of STAS on three histological types of NSCLC in a total of 3,754 patients from 14 studies. Their review showed that STAS positivity was associated with worse recurrent-free survival (RFS). Subgroup analysis also confirmed the results, and the presence of STAS was found to be significantly associated with inferior RFS in adenocarcinoma, SCC, and lung pleomorphic carcinomas. The OS, as the secondary outcome of the review, was inferior in adenocarcinoma patients with the STAS positivity. However, there was no significant difference in the OS of the other STAS-positive subgroups. Taken together, they suggested that the presence of STAS was a potential prognostic factor for patients with NSCLC; however, the prognostic impact of STAS positivity in the resection margin was still unclear and further studies were needed to be able to determine the extent of resection.

Ren et al.[19] examined the prognostic impact of STAS in 752 Stage IA NSCLC patients who underwent lobectomy or SR. In the multivariable analysis adjusted for various variables, STAS was not a prognostic predictor of RFS or OS in the lobectomy cohort. However, it showed a significantly worse prognosis in the SR cohort both in terms of RFS (hazard ratio [HR]: 3.529, $p<0.001$) and OS (HR: 4.547, $p<0.001$). Although the authors reinforced their results by adjusting potential confounders in the assessment of RFS and OS, the STAS positivity was significantly higher in high-grade tumors in both cohorts.

In a very well-designed study with an extensive adjustment for confounders, Eguchi et al.[5] investigated the impact of STAS on procedure-specific outcomes (lobectomy *vs.* SR) and the effect of surgical margin/tumor (M/T) diameter ratio in STAS positivity. They analyzed 1,497 patients with Stage IA NSCLC who underwent lobectomy or SR after propensity score matching. They showed that, in STAS-negative patients, there was no significant difference in the cumulative incidence of recurrence (CIR) between lobectomy and SR. Nevertheless, in patients with STAS, SR was significantly associated with a higher risk of recurrence than lobectomy (five-year CIR, 39% *vs.* 16%, respectively; $p<0.001$). Similar results were also reported in lung cancer-specific cumulative incidence of death (LC-CID) analyses. They also

implemented additional multivariable analyses using the same variables in two separate cohorts stratified according to the STAS status. The SR was independently associated with both recurrence and lung cancer-specific death in STAS-positive patients (HR for recurrence: 2.84, p<0.001; HR for lung cancer-specific death: 2.63, p=0.021). Besides, in STAS-positive patients, recurrences after SL resection were associated with a M/T ratio of <1. However, the margin/STAS analysis was not adjusted for any confounders. As a result, the authors concluded that, in early-stage STAS-positive NSCLC patients, lobectomy should be the standard treatment.

STAS and Thoracic Surgeon

The important question for thoracic surgeons in the evolution of this phenomenon would be whether STAS affects the choice of the extent of resection for Stage I NSCLC. In other words, should we perform lobectomy instead of SR in STAS-positive patients? In this context, the most optimal outcome would possibly be the incidence of recurrence. The RFS is unclear, as it also includes non-cancer events. The association of STAS with multiple negative prognostic factors underlines the need for healthy adjustment for confounders. In most recent studies, as mentioned above, the STAS positivity is associated with worse RFS and higher recurrence rates after SR. Although this association is mostly persistent despite multivariate adjustment, the degree of accounting for confounders is usually poor.

In addition, there is a couple of problems with STAS that needs to be addressed. First, our understanding of the biological cause of STAS is in a nascent stage. More data are required to assume whether STAS reflects the host-tumor interaction. Second, there is an assumption that STAS may be a manifestation of artifacts caused by the mechanical spread of dissociated tumor cells by the knife surface during slide preparation.[20,21] However, most studies have proven that STAS is a clinically significant biological phenomenon that has a prognostic impact on all types of lung cancer.[1,5,6,14,18,22] Third, does the frozen section (FS) is reliable enough to recognize STAS intraoperatively and guide surgeons to decide the extent of the resection? In the literature, sensitivity and specificity of FS ranged from 59 to 86% and 74 to 100%, respectively.[15] Walts et al.[23] reported that there were insufficient data in the literature to support intraoperative detection of STAS as a useful predictive feature to help surgeons to decide the extent of the resection. However, Eguchi et al.[5] showed promising results regarding FS analysis with relatively better sensitivity (71%) and similar specificity (92%) compared to the literature, for detecting STAS. They concluded that FS could guide surgeons to decide the most appropriate type of resection for patients with early-stage lung cancer. Nevertheless, their results regarding the FS analysis should be validated by further studies.

In conclusion, spread through air spaces is a biologically important phenomenon and is associated with unfavorable patient outcomes in non-small cell lung cancer. Sublobar resection is associated with a significantly higher risk of recurrence and lung cancer-specific cumulative incidence of death in patients with spread through air spaces. Although the most recent data supports lobectomy over limited resection in spread through air spaces-positive Stage I non-small cell lung cancer, further studies with a better adjustment of confounding factors are needed to confirm these results. Future studies would potentially be helpful to detect a precise and safer margin distance and would also guide surgeons to consider postoperative adjuvant treatment options in patients with spread through air spaces-positive tumors.

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