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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of STAS Positivity in Lung Cancer

Akciğer Kanserinde STAS Pozitifliğinin Etkisi

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ABSTRACT

Aim: The spread through air spaces (STAS) phenomenon, which describes the presence of tumor cells in the air spaces of lung cancer, has been associated with an increased risk of local recurrence. We performed retrospective analyses to examine the presence of STAS in lung cancer and to evaluate its clinical results and its relationship with clinicopathological parameters.

Material and Method: A total of 149 surgically resected lung cancer cases were analyzed retrospectively. Detailed analyses were performed on demographic- radiological-clinical-histological features.

Results: The mean age of the patients was 63 (IQR=11; range, 22–81), among whom 31 were female and 118 were male. The incidence of STAS was not different between the histological groups (p=0.427). There was no difference between SUVmax value in STAS-positive and negative patients (p=0.970). The recurrence rate, survival, and median tumor size were not different from each other in the STAS-positive and STAS-negative groups (p=1,000, p=0.086, p=0.292, respectively).

Conclusion: STAS is an independent risk factor for poor prognosis. Therefore, it may be possible to provide more personalized information by using clinicopathological markers that will facilitate preoperative prediction of STAS presence.

Keywords: Non-small cell lung cancer, spread through air space, prognosis

ÖZ

Amaç: Akciğer kanserinde hava yollarında tümör hücrelerinin varlığını tanımlayan hava yollarına yayılma (STAS) fenomeni, artmış lokal nüks riski ile ilişkilendirilmiştir. STAS'ın klinikopatolojik parametrelerle ilişkisini değerlendirmek için retrospektif olarak akciğer kanseri için cerrahi yapılan hastaları inceledik.

Gereç ve Yöntem: Cerrahi olarak rezeke edilen toplam 149 akciğer kanseri olgusu retrospektif olarak analiz edildi. Demografik-radyolojik-klinik-histolojik özellikler üzerinde ayrıntılı analizler yapıldı.

Bulgular: Hastaların ortalama yaşı 63 (IQR=11; dağılım, 22-81) olup, 31'i kadın ve 118'i erkekti. STAS insidansı histolojik gruplar arasında farklı bulunmadı (p=0.427). STAS-pozitif ve negatif hastalarda SUVmax değeri arasında fark yoktu (p=0.970). STAS-pozitif ve STAS-negatif gruplarda nüks oranı, sağkalım ve medyan tümör boyutu birbirinden farklı değildi (sırasıyla p=1.000, p=0.086, p=0.292).

Sonuç: STAS kötü prognoz için bağımsız bir risk faktörüdür. Bu nedenle, STAS varlığının ameliyat öncesi tahminini kolaylaştıracak klinikopatolojik belirteçler kullanılarak surveye katkı sağlayacak daha kişiselleştirilmiş bilgi elde etmek mümkün olabilir.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, hava boşluğuna yayılım, prognoz

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths, and surgery is still the gold standard of treatment. The spread through air spaces (STAS) phenomenon, first described by Kadota et al. in 2015, is defined as the spread of tumor cells in lung cancer through the air spaces outside the main tumor (1). STAS has been found to be an important predictive factor for local recurrence. Although STAS was initially defined in adenocarcinomas, it is now detected in all types of lung cancer (2). Its importance as a prognostic factor has been demonstrated by several survey studies (3-6).

The aim of our study is to examine the presence of STAS and to evaluate its clinical results and its relationship with clinicopathological parameters.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: E1-20-817). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data from patients who underwent a surgical resection for lung cancer in our clinic between 2019 and 2022 were retrospectively evaluated. Patients whose complete records could not be located, who were excluded from follow-up, or who had M1 or M2 metastases according to the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control's (UICC) 8th tumor–node–metastasis (TNM) staging classifications were excluded from the study. Patient data collected included age, gender, presence and type of peroperative diagnostic procedures, pathology, type of operation, survival, recurrence, whether they received preoperative chemotherapy, TNM stage, whether mediastinoscopy was performed, STAS positivity, visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, evaluation for perineural invasion, and alveolar/bronchial wall invasion.

The patients were followed up for an average of 12.66 months (0.17–41.97 months).

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY). The conformity of the variables to the normal distribution was examined using visual histograms, probability charts, and analytical methods (Kolmogorov–Smirnov and Shapiro–Wilk tests). Descriptive analyses were made using median and interquartile range for non-normally distributed variables.

Because it was determined that the survey and SUVmax did not show normal distributions, these variables were compared between the STAS and lymphovascular invasion groups using the Mann–Whitney U test.

Similarly, because it was determined that the age variable was not normally distributed, the assessment of whether this parameter differed between histological groups was conducted using the Kruskal–Wallis test. STAS, age group, gender, operation type, visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, perineural invasion, alveolar–bronchial invasion, and TNM stages were determined using cross tables. Whether there was a difference between the groups in terms of these frequencies was compared using chi-square or Fisher tests (in cases where the values observed in the cells did not meet the chi-square test assumptions). The correlation coefficient and statistical significance between non-normally distributed age and tumor size and the survey were calculated with Spearman's test. A receiver operating characteristics (ROC) curve analysis was used to determine whether tumor size was a diagnostic decision-maker in predicting STAS positivity. For statistical significance, the total type 1 error level was used as 5%.

RESULTS

Surgical resection was performed in a total of 149 patients due to lung cancer during the study period. Clinicopathological features of patients are listed in **Table 1**. The mean age of the patients was 63 (IQR=11; range, 22–81), among whom 31 were female and 118 were male. The tumors of 87 patients were located in the right hemithorax, while 62 patients had tumors in the left hemithorax. The median survival of the patients was 12.66 months (minimum 0.17 months, maximum 41.96 months, IQR 15.72). Survival was not different between male and female patients (p=0.272), and the rate of recurrence was not different between male and female patients (p=0.580). Age was not different between stages (p=0.851). The incidence of STAS was not different between the genders (p=0.673). There were 11 patients who had received chemotherapy before the operation. Mediastinoscopy was performed for mediastinal staging before resection in 6 patients. During the follow-up period, 13 patients (8.72%) died, and recurrence was detected in 4 patients (2.7%).

While the median SUVmax value in STAS-positive patients was 12.3 (IQR, 9.09), it was 11.5 (IQR, 13.24) in STAS-negative patients (p=0.970).

In the present study, a bronchoscopic biopsy was performed in 60 patients (40.3%) preoperatively, and transthoracic fine needle aspiration biopsy was performed in 60 patients (40.3%). Because a diagnosis could not be obtained through preoperative diagnostic procedures in 29 patients (19.4%), a lung resection was performed in these patients after a perioperative wedge resection with frozen sections was examined.

Table 1. Clinicopathological features of patients	
Pathological features (n/%)	
STAS positivity	43/28.9
Visseral pleura invasion	47/31.5
Parietal pleura invasion	15/10.1
Lymphovascular invasion	73/48.9
Perineural invasion	33/22.1
Alveolar–bronchial invasion	73/48.9
Surgery (n/%)	
Lobectomy/pneumonectomy	116/77.9
Segmentectomy/wedge resection	9/16.1
Extendend resections	24/6
Histopathological type (n/%)	
Squamous Cell Carcinoma	69/46.3
Adenocarcinoma	50/33.6
Neuroendocrine Carcinoma	10/6.7
Carcinoid Tumor	6/4
NOS	4/2.7
Other	10/6.7
Total	149/100
*STAS, spread through air spaces	

Age was different between the histological groups, p=0.041. Age was significantly younger in the carcinoid group (p=0.023). There were no statistically significant differences in the incidence of STAS between histology groups (p=0.427).

The patients were also sorted into two groups, as <60 years old and ≥60 years old. There were 49 patients (32.9%) aged <60 years and 100 patients (67.1%) aged ≥ 60 years in these groups. The incidence of STAS was not different between the two groups (p=0.227). Likewise, the parietal pleural invasion rate, alveolar–bronchial invasion rate, perineural invasion rate, and visceral pleural invasion rate were not different from each other (p=0.969, p=0.725, p=0.720, and p=0.195, respectively). However, the lymphovascular invasion rate was different (p=0.015). Survival was found to be lower in the group ≥ 60 (p=0.027), but the rate of recurrence was not different (p=1.000).

A very strong negative correlation was found between age and survey (p=0.005, r=0.228). In addition, the incidence of STAS was not different between the histological groups (p=0.427).

The rates of visceral pleural invasion, parietal pleural invasion, lymphovascular invasion, and perineural invasion were statistically different between the STAS-positive and STAS-negative groups (p<0.001, p=0.037, p<0.001, p=0.017), while the rates of alveolar–bronchial invasion were not statistically different (p=0.289).

There were no statistically significant differences in STAS incidence and parietal pleural invasion rates between stages (p=0.372, p=0.061). However, the rates of visceral pleural invasion, lymphovascular invasion, perineural invasion, and alveolar–bronchial invasion were different from each other (p=0.002, p<0.001, p<0.001, and p=0.002, respectively).

The most common visceral pleural invasion was detected as Stage 3A. The most common lymphovascular invasion was detected as Stage 2B and Stage 3A. The most common perineural invasion was detected as Stage 2B and Stage 3A. The stage with the most common alveolar–bronchial invasion was determined to be Stage 3A. There were no differences in STAS rates according to the operation type (p=0.402).

The recurrence rate, survival, and median tumor size were not different from each other in the STAS-positive and STAS-negative groups (p=1,000, p=0.086, p=0.292, respectively). In addition, no significant cut-off value was found in the groups for tumor size (p=0.293).

Survival was not different between the groups with and without lymphovascular invasion, parietal pleural invasion, or visceral pleural invasion (p=0.314). However, survival was different between patients with and without alveolar–bronchial invasion (p=0.024), with median survival found to be high in patients without invasion. The incidence of recurrence was not different between patients with and without lymphovascular invasion, parietal pleural invasion, visceral pleural invasion, alveolar–bronchial invasion, or perineural invasion (p=0.360 p=0.349, p=0.591, p=0.360, and p=1,000, respectively). No correlation was found between tumor size and the survey (p=0.555).

DISCUSSION

The issues of how STAS affects diagnosis and treatment parameters and its relationship with histopathology remain up-to-date (7). Similar to the literature, no significant difference was found between patients with and without STAS in terms of age, gender, tumor size, and tumor location (8). It has even been reported that SUVmax is a valuable indicator for the prediction of STAS in clinical Stage I lung adenocarcinoma (9). In contrast to these results, we concluded in our study that SUVmax values were not a sufficient parameter to predict STAS positivity.

In studies that aimed to create a prediction model using radiomic values, it was suggested that those values can guide the preoperative prediction of STAS in early stage lung adenocarcinoma and related surgeries (10). In fact, there was a study that stated there was good calibration in the nomogram prediction model of STAS in clinical Stage I non-small cell lung cancer (NSCLC) (11). However, these studies were retrospective, which can lead to selection bias, and they were conducted in a limited number of centers and with a limited number of patients. Also, preoperative investigations of patients were heterogeneous. Therefore, attempts to establish modeling and pre-treatment prediction guides in other studies will continue.

In a study investigating whether percutaneous needle biopsy and bronchoscopic biopsy cause tumor dissemination via STAS, it was not shown that preoperative biopsy increased STAS formation, postoperative recurrence, or death in patients with Stage I NSCLC (12). Similarly, in our study, the incidence of STAS was not different between patients who underwent preoperative invasive transthoracic biopsy or bronchial biopsy and those who did not undergo diagnostic procedures. Therefore, we disagree with the concern that commonly used preoperative diagnostic procedures may lead to STAS.

Although the incidence of STAS was not found to be different between histopathological subtypes in our study, the difference can be revealed more clearly with larger series. STAS has been reported as an independent factor of poor prognosis in squamous cell carcinoma and a factor reflecting tumor aggressiveness associated with the presence of other poor prognostic factors, such as embolism and pleural invasion (13-15).

NSCLCs with STAS have higher rates of visceral pleural and lymphovascular invasion than those without STAS (8). Similarly, in our study, we found that all invasions were more common in the STAS-positive group. However, in our study, we concluded that this trend was not reflected in alveolar or bronchial invasion. If STAS is defined by cells that break off from the main tumor and fall into the bronchus and alveoli with certain signals, it would be expected that alveolar and bronchial invasion would be high in the STAS-positive group. This result leads us to the conclusion that some aspects of the mechanism of STAS formation remain obscure.

STAS positivity has the capacity to predict the extent of surgical resection, regardless of lymph node status (16). It has been stated that in the future, the detection of intraoperative STAS will become routine thanks to the development of technological techniques (17,18). The fact that the recurrence rate was not different between the STAS-positive and STAS-negative groups in our study may be due to the short follow-up period.

We believe that STAS-positive patients, regardless of histopathology or stage, should be closely monitored for recurrence. We also believe that because of the high risk of recurrence, patients should be evaluated more carefully for sublobar resections.

There were some limitations in our study. First, this was a retrospective design, which could have led to selection bias. Other limitations include heterogeneity and the limited number of patients. Also, the follow-up period was short, and mutational information about the tumors was not investigated.

CONCLUSION

STAS is a risk factor for recurrence after resection in NSCLC. Currently, there is no biomarker that can predict STAS positivity. Thanks to the increasing number of studies in this field, it may be possible to determine an appropriate surgical resection width that could increase recurrence-free survival.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: E1-20-817).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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