Differential Impact of Spread Through Air Spaces on Subtypes of Early-stage Lung Cancer

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ABSTRACT

Objective: To investigate the prognostic significance of STAS (Spread through air spaces) and its effect on survival in the various types of non-small cell lung cancer (NSCLC).

Study Design: Descriptive analytical study.

Place and Duration of the Study: Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkiye, between 2018 and 2021.

Methodology: Early-stage lung cancer patients who underwent lobectomy were included. STAS was defined as presence of tumour cell clumps, solid nests or set of single cells located in airway spaces apart from the main tumour border and determined by pathological work-up. The clinical significance of STAS was investigated by means of histopathological subtype, tumour size, and maximum standardised uptake value (SUVmax) on PET-CT scan in early-stage lung cancer by grouping it as adenocarcinoma and non-adenocarcinoma. Five-year overall and disease-free survival, and recurrence were the outcome measures.

Results: A total of 165 patients were included in the study. No recurrence was observed in 125 patients, 40 patients developed recurrence. Five-year overall survival (OS) was 69.6% in STAS (+) cohort and 74.5% in STAS (-) cohort (p=0.88). Five-year disease-free survival (DFS) was 51.1% in STAS (+) cohort and 73.1% for STAS (-) cohort (p=0.034). While the absence of STAS in the adenocarcinoma group was associated with better DFS, lower SUVMax and smaller tumour size, similar results were not found to be at statistically significant level in the non-adenocarcinoma group.

Conclusion: STAS positivity makes a difference in DFS, tumour size and SUVmax, especially in adenocarcinoma, however, it does not create a significant difference in survival or clinic pathological features in the non-adenocarcinoma.

Key Words: *Lung Cancer, Lobectomy, Spread through air spaces, Survival, Prognosis.*

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INTRODUCTION

Anatomical resection with mediastinal lymph node dissection is the gold standard treatment modality in early-stage lung cancer. Although complete resection is the first choice of treatment, approximately 30% develop recurrences.[1] Therefore, it is necessary to investigate the risk factors for recurrence in such patients. Even for the early-stage lung cancer, tumour invasion indicators such as lymphovascular invasion, pleural invasion, and stromal infiltration have been proven to be associated with poor prognosis.[2] Spread through air spaces (STAS) is also another newly-introduced sign of tumour invasion.[3] STAS is thought to be an indicator of poor prognosis, however, it has not been clearly demonstrated yet, and a consensus has not been achieved on studies on this topic.

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STAS defines tumour cell clumps, solid nests or a set of single cells located in airway spaces apart from the main tumour border. It was first described by Kadota *et al.* in adenocarcinomas in 2015.[4] This phenomenon was previously referred to as aerogenous dissemination and tumour islands,[5,6] but the final nomenclature by Kadota *et al*. has been widely accepted. Although it has been considered as a kind of artefact by some authors,[7] it was proposed to be introduced as a novel invasion pattern for adenocarcinoma in the lung cancer classification in 2015.[8] Tumour budding was defined as the presence of isolated tumour cells fewer than five in the stromal area at the outer edge of the tumour. While tumour budding exists in the stroma of the invasive tumour, STAS is located in the alveolar parenchymal spaces.[9]

Although there are publications reporting that the presence of STAS is associated with poor prognosis in resected lung cancer cases, a comparison of the effect of STAS on separate subtypes has not yet been made. This study aimed to determine the impact of STAS on the subtypes of early-stage lung cancer in terms of survival and recurrence.

METHODOLOGY

Patients who were operated for primary lung cancer in Kartal Dr. Lutfi Kirdar City Hospital Thoracic Surgery clinic, between January 2018 and August 2021 were enrolled retrospectively. Among these patients, those with <5 cm tumour, pN0 patients, and those who had lobectomy were included. In order to form a homogenous group, patients who underwent surgical resection other than lobectomy, who received adjuvant therapy, who were advised but did not consent to receive adjuvant therapy, patients with additional malignancy, and patients whose medical records were not obtained were excluded from the study. The prognostic efficacy of STAS was investigated by grouping the early-stage lung cancer patients who underwent lobectomy based on the presence of STAS, histopathological subtype (as adenocarcinoma and non-adenocarcinoma) and tumour size. The effect of STAS on survival and clinicopathological features was compared for each group.

Pathology slides were examined by a thoracic pathology specialist with an Olympus BX51 microscope. STAS was confirmed when tumour islands located in the normal alveolar spaces apart from tumour margin were identified. STAS was distinguished from macrophages in alveolar spaces by their morphological features. While nuclear atypia and increased nucleus/cytoplasm ratio were encountered in tumour cells, macrophages had small nuclei and contained foamy vacuoles and carbon pigment in their cytoplasm. Tumour budding was spotted in stromal areas but STAS in alveolar spaces apart from the main tumour island.

In the postoperative period, the patients were scanned in the outpatient clinic by chest computed tomography every 6 months for the first 3 years and then annually until the 5th year. Recurrence was confirmed by radiological work-up and Positron Emission Tomography (PET) findings or biopsy results. Disease-free survival (DFS) is determined as the time interval between the operation and the first detected recurrence. Overall survival (OS) is determined as the time between operation and death. Patients who developed recurrences were promptly referred to medical oncology or radiation oncology departments to get their appropriate treatment initiated. The survival of the patients was investigated by examining the outpatient medical forms and by the contacting the patients or their relatives by phone.

This study was approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with number 2022/514/232/5. A detailed informed consent form was obtained from each patient prior to operation.

Chi-Square and Fisher's Exact test (when expected value <5) were used to compare categorical data which are expressed as counts and percentages. Student's t-test was preferred for comparing continuous variables which are expressed as mean and standard deviation. Kaplan-Meier method was used to calculate OS and DFS. Statistical significance was determined by log-rank test. The p-values below 0.05 were considered to be statistically significant. Statistical analysis was performed with SPSS (Statistical Program for Social Sciences 25.0; IBM Corporation, Armonk, NY, USA).

RESULTS

Between January 2018 and August 2021, 402 patients underwent lung resection for primary lung cancer. A total of 165 patients who met the inclusion criteria were reviewed. Among those, 50 (30.3%) patients were females and 115 (69.7%) were males. The distribution of the patients included in the study according to the stage and histopathological subtype are displayed in Table I.

Table I: Distribution of patients by histopathological subtype and stage.

	Number (n)	Percentage (%)
Histopathological subtype		
Adenocarcinoma	97	58.8%
Non-Adenocarcinoma	68	41.2%
Squamous Cell Carcinoma	49	29.7%
Large Cell Carcinoma	3	1.8%
Carcinoid tumour	4	2.4%
Pleomorphic Carcinoma	3	1.8%
Large Cell Neuroendocrine Carcinoma	2	1.2%
Adenosquamous Carcinoma	7	4.2%
Stage		
1A	116	70.3%
1B	31	18.8%
2A	18	10.9%
Total	165	100.0%

Of the patients included in the study, 59 (35.7%) were STAS (+) and 106 (64.3%) were STAS (-). STAS positivity was observed in 36% of female patients and 35.7% of male patients. The mean age of all cohort is 63.2±8.5, the mean age of the STAS (+) group was 62.6±8.2, and the mean age of the STAS (-) group is 63.6±8.7 (p=0.46).

Recurrence is observed in a total of 40 (24.2%) patients. While the recurrence rate is 32% in STAS (+) group, it is 19.8% in STAS (-) group (p=0.075). When only adenocarcinoma patients were examined, recurrence rates of STAS (+) and (-) groups are 34.1% and 17.8%, respectively (p=0.06). The recurrence rate is determined as 27.7% for STAS (+) group and 27.5% for STAS (-) group in non-adenocarcinoma patients (p=0.6).

The sites of recurrence of the patients who developed recurrence are shown in Table II.

Detailed comparison of OS, DFS, recurrence, maximum standardised uptake value (SUVmax) and size according to STAS in the whole group, in the adenocarcinoma group and in the non-adenocarcinoma group is depicted in Table III.

Patients were grouped based on histopathological subtypes as adenocarcinoma and non-adenocarcinoma. Among STAS (+) group, 5-year DFS for adenocarcinoma was 51.1% and 5-year DFS for non-adenocarcinoma was 54.2% (p=0.67). The 5-year OS for those patients were 70.0% and 69.1%, respectively (p=0.47). The 5-year DFS for STAS (-) adenocarcinoma group was 77.9% and 69.5% for STAS (-) non-adenocarcinoma group (p=0.49). The 5-year OS for STAS(-) adenocarcinoma and non-adenocarcinoma were 86.2% and 63%, respectively (p=0.036).

Table II: Sites of recurrence according to STAS in patients with recurrence.

			Site of Recurrence				Total
			Local (Lungmediastinum)	Bone	Cranium	Other	
STAS	Present	Number	12	2	3	2	19
		%	63.2%	10.5%	15.8%	10.5%	100%
	Absent	Number	16	2	2	1	21
		%	76.2%	9.5%	9.5%	4.8%	100%
Total		Number	28	4	5	3	40
		%	70%	10%	12.5%	7.5%	100%

STAS: Spread through air spaces

Table III: Comparison of OS, DFS, recurrence, SUVmax, and size according to STAS in the whole group, in the adenocarcinoma group, and in the non-adenocarcinoma group.

	5-year OS	5-year DFS	Recurrence	SUVMax	Size (mm)
All cohort	72.5%	65.5%	24.8%	8.0±5.0	24.8±11.3
STAS (+)	69.6%	51.1%	32.0%	8.3±5.8	26.2±11.6
STAS (-)	74.5%	73.1%	19.8%	7.8±4.7	24.6±11.4
p-value	0.88	*0.034*	0.075	0.57	0.39
Adenocarcinoma	78.7%	66.9%	24.7%	7.0±5.3	23.7±11.0
STAS (+)	70%	51.1%	34.1%	8.4±6.5	26.5±11.7
STAS (-)	86.2%	77.9%	17.8%	6.0±3.9	21.7±10.2
p-value	0.41	*0.028*	0.06	*0.044*	*0.031*
Non-adenocarcinoma	64.3%	66.2%	23.5%	9.3±4.5	26.2±11.7
STAS (+)	69.1%	54.2%	27.7%	8.0±4.0	26.1±11.8
STAS (-)	63.0%	69.5%	22.0%	9.6±4.7	26.2±11.8
p-value	0.94	0.52	0.6	0.22	0.98

DFS: Disease-free survival; OS: Overall survival; STAS: Spread through air spaces; SUVMax: Maximum standardised uptake value. Kaplan-Meier method is used to compare 5-year OS and DFS, Chi-Square test is used to compare recurrence, Student's t-test is used to compare SUVMax and Size (mm).

There were 49 patients diagnosed with squamous cell carcinoma (SCC). STAS rate was higher in adenocarcinoma than in SCC (42.3% *vs.* 21.2%, p=0.018). STAS positivity rate of adenocarcinoma was also higher than non-adenocarcinoma (42.3% *vs.* 26.4%, p=0.037).

The mean SUVmax value was 7.0 for the adenocarcinoma group and 9.3 for the non-adenocarcinoma group (p=0.013). Among STAS (-) patients, the mean SUVmax was 6.0 in the adenocarcinoma group and 9.6 in the non-adenocarcinoma group (p=0.001). In STAS (+) group, these values were 8.47 in adenocarcinoma and 8.0 in non-adenocarcinoma (p=0.8).

DISCUSSION

In this study, the clinical importance of STAS was investigated. STAS positivity was 35.7% in patients operated for early-stage non-small cell lung carcinoma (NSCLC). Other studies on this subject reveal similar rates of STAS presence in early-stage lung cancer.[6,10,11] Such a high positivity rate raises the question whether there is a need for extra treatment such as adjuvant chemotherapy following surgery in STAS (+) patients, and if there is such a need, which subtype would be a better candidate for it. There are some studies expressing STAS as a phenomenon that may alter the indication of adjuvant chemotherapy in the postoperative follow-up algorithm or mandate lobectomy rather than segmentectomy even for tumours smaller than 2 cm.[12-14] However, the question whether the presence of STAS has a similar effect on each and every NSCLC case has come to the agenda.

It is seen that the effect of STAS on survival and clinic pathological features show different results in various studies. Kadota *et al*. stated that STAS positivity had no effect on DFS in adenocarcinoma patients who underwent lobectomy.[4] However, the number of publications that disagree with this statement is higher. When the literature is examined, many reports specifying the negative effect of STAS on DFS and/or OS can be noticed.[3,15-17] One of the facts that have emerged recently about STAS is that it affects the survival of resected primary lung cancer. In the present study, evaluation of OS according to STAS presence reveals that the OS of STAS (+) patients are slightly poorer than STAS (-) patients. The difference between DFS's is greater and reaches statistical significance. Similar survival rates are also seen in the literature.[11] While there is no significant difference between OS's, there is a significant difference between DFS's, indicating that STAS presence does not affect OS but affects DFS. Shiono *et al*. also stated that STAS positivity in early-stage NSCLC affects DFS rather than OS.[18] Considering that patients have promptly been referred to chemotherapy following the development of recurrence, it can be said that STAS (+) tumours benefit from chemotherapy. Similarly, STAS positivity in adenocarcinoma did not make a significant difference in OS, but it made a significant difference in DFS. Difference in recurrence rates created by STAS presence in adenocarcinoma being closer to statistical significance than non-adenocarcinoma supports this finding (p=0.060 *vs.* 0.075). The presence of STAS in the non-adenocarcinoma cohort was associated with a less favourable prognosis which did not make statistical significance in survival and recurrence rate. It was noticed that the difference created by STAS in the adenocarcinoma group was greater than in the non-adenocarcinoma group. Since adenocarcinoma is the predominant subtype in the study, the effect of STAS on survival of all groups may have been affected by the adenocarcinoma group.

When only STAS (+) patients were examined, no significant difference was observed between adenocarcinoma and non-adenocarcinoma groups in terms of DFS and OS. On the other hand, it was observed that DFS of STAS (-) adenocarcinoma group was similar to that of STAS (-) non-adenocarcinoma group, but STAS (-) adenocarcinoma was significantly higher in OS. Thus, it can be said that in STAS (-) status, adenocarcinoma is associated with a better prognosis than other subtypes.

No significant difference was observed between the STAS (+) and STAS (-) groups in SUVmax values in NSCLC. STAS positivity was associated with higher SUVmax value in adenocarcinoma patients. In STAS (+) group, adenocarcinoma is related with higher mean SUVmax, on the other hand, in STAS (-) group, it is related with significantly lower SUVmax. Considering that the SUVmax value is directly proportional to the prognosis,[19] this finding supports that STAS (-) adenocarcinoma has a better prognosis than STAS (-) non-adenocarcinoma. In addition, the fact that STAS presence not making a significant difference in SUVMax in all cohort but causing significant difference in the adenocarcinoma group also indicates that STAS is more important in adenocarcinoma. Studies on SUVmax according to STAS presence also reveal that STAS positivity of adenocarcinoma rather than SCC is related with significant difference in SUVmax.[20]

In this study, STAS presence caused a significant difference in tumour size only in the adenocarcinoma group but did not make a significant difference in the non-adenocarcinoma group. Similar studies on this subject also show that the presence of STAS makes a significant difference in adenocarcinoma, but does not lead to a significant difference in other subtypes.[21]

There are several limitations in this study. First, this study was designed as a retrospective analysis. Fortunately, patient records are kept in detail and are meticulously archived. Second, the number of patients is limited. Nevertheless, it is able to display that STAS presence creates a statistically significant difference in SUVMax, tumour size, and DFS, especially in adenocarcinoma compared to non-adenocarcinoma early-stage lung cancer.

CONCLUSION

STAS presence was associated with recurrence in the whole population. The negative prognostic effect on DFS was greater in adenocarcinoma. STAS presence in adenocarcinoma significantly related with higher SUVMax and greater tumour size. On the other hand, it did not significantly alter survival and clinic pathological features in the non-adenocarcinoma group.

ETHICAL APPROVAL:
This study is approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with Number. 2022/514/232/5.

PATIENTS' CONSENT:
A detailed informed consent form was obtained from each patient prior to operation.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
BC: Conception, design, data collection, analysis and interpretation, and drafting.
BC, GG, SK: Data collection, analysis and interpretation, and drafting.
MB: Analysis and interpretation and drafting.
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