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Original Article

Association between Histologic Subtypes of Non-Small Cell Lung Cancer and Survival: Retrospective Cohort Analysis of 1887 Patients

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ABSTRACT

Objective: Histologic subtypes of non-small cell lung cancer (NSCLC) may be associated with the outcome of the disease. Adenosquamous carcinoma, a rare but aggressive tumor, has been related to poor survival rates. This study aimed to evaluate the survival rates of the patients with histologic subtypes of NSCLC after surgical treatment.

Methods: A single-center retrospective study for patients with NSCLC who underwent surgical treatment was performed between 2000 and 2009. The histologic types were grouped as adenocarcinoma (Group A), squamous cell (Group S), and adenosquamous carcinoma (Group AS). Patient demographic and clinical characteristics and survival data were collected. The primary outcome was the rate of patients who survived the post-operative 5 years.

Results: A total of 1887 patients (Group A: 834 (44.2%), Group S: 996 (52.8%), and Group AS: 57 patients (3.0%) were included in the study. Lobectomy was the most frequent resection performed in 74%, 71%, and 63% of the cases in Groups A, S, and AS. In-hospital mortality rates in the groups were similar (p=0.555). Five-year survival rates were 41%, 47%, and 36% in Groups A, S, and AS. The rate of 5-year survival in Group AS was significantly lower than in Group A (p=0.04) and Group S (p=0.001). Group S had a significantly higher rate of 5-year survival than Group A (p=0.001).

Conclusion: Adenosquamous histology was the worst type of NSCLC regarding survival outcomes. Patients with squamous histology fare better than those with adenosquamous and adenocarcinoma histologic subtypes.

INTRODUCTION

Lung cancer is one of the most frequent causes of death among all malignancies throughout the world.[1,2] Besides the improvements in screening programs and early diagnosis leading to primary resection for operable candidates, the long-term survival of patients with lung cancer shows variations depending on many patients and tumor-related variables.[3]

Non-small cell lung cancer (NSCLC) comprises over 80% of all lung cancer cases.[2,4] Surgery is the mainstay treatment modality for most cases with NSCLC.[4] Although lobectomy is the most frequently performed type of surgery in these patients, pneumonectomy and segmentectomy are the other choices.[5–7] The previous studies have reported different survival outcomes for different types of surgical resections.[5,8,9]

Histopathological typing is the gold standard diagnostic method for many diseases.[10] The crucial differences in the genetic and microenvironments of tumors originating from histological characterization may affect the efficacy of treatment modalities.[2,11] The previous studies reported that adenosquamous and squamous carcinoma have aggressive behavior with poorer survival than adenocarcinoma.[12–14] The clinicopathological characteristics and their associated prognosis may vary according to the different histologic types of NSCLC.[12] Nevertheless, the type of histology as a possible risk factor impacting survival has not been studied in detail.[15]

We hypothesized that adenosquamous histology of NSCLC has poorer survival after curative intent surgery than adenocarcinoma and squamous carcinoma types. In this study, we aimed to evaluate the survival outcomes of the patients with three main types of NSCLC follow-

ing surgical treatment in the real-world setting among the Turkish population.

MATERIALS AND METHODS

Study

A single-center retrospective analysis of all patients who underwent surgical treatment for NSCLC in a thoracic surgery clinic at Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital was performed between 2000 and 2009. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

The researchers agreed to apply the principles of the Helsinki Declaration. The written informed consent could not be taken from the patients due to the retrospective design of the study and the unanimity of data.

Patients

All consecutive NSCLC patients who underwent lobectomy, pneumonectomy, segmentectomy, and wedge resection with a curative intent through thoracotomy were evaluated. The histologic types of adenocarcinoma, squamous, and adenosquamous carcinoma were included in the study. The exclusion criteria were other histological types (large cell carcinoma, carcinoid tumor, and carcinosarcoma), unresectable tumors, and missing data. Finally, 1887 patients were analyzed in the study.

A standardized pre-operative assessment was applied to all patients. This strategy included all patients' respiratory function tests, chest computed tomography, and the respiratory tree's fiber-optic bronchoscopy. If necessary, we obtained magnetic resonance imaging of the brain and positron emission tomography scans (as a routine procedure after 2005). Mediastinoscopy, mediastinotomy, or video-assisted thoracic surgery were performed in selected cases where other interventions, such as fiber-optic bronchoscopic or percutaneous transthoracic biopsy procedures, were non-diagnostic for NSCLC. The neoadjuvant and adjuvant treatment modalities were determined based on the clinical tumor/node/metastasis status in the multidisciplinary oncology tumor board of the hospital. The operative details were described previously.[4,7,9,16] The staging was performed using the final pathology report and determined based on the TNM classification based on the 7th American Joint Committee on Cancer Staging Manual.[13]

The patients were grouped based on the different histologic types of NSCLC as adenocarcinoma (Group A), squamous carcinoma (Group S), and adenosquamous carcinoma (Group AS).

Variables

We retrospectively collected the patients' demographic and clinical characteristics using the hospital information system and the patient's medical files. The clinical data included the histological type, diameter, TNM stages, surgical modality, and post-operative complications and mortality.

Follow-up

Regardless of adjuvant therapy, the follow-up data were collected from the records of the post-operative outpatient visits performed every 3 months for the first 2 years and every 6 months for the following years. The survival data were collected through outpatient visits, telephone interviews, or the national population registry system.

The patients who died within the post-operative 1st month secondary to the surgery-related morbidity were regarded as post-operative mortality and were not included in the overall survival analysis. The rate of patients who survived the post-operative 5 years was calculated.

Statistical analysis

The primary outcome was the 5-year survival rate. The patients were stratified according to different histologic subtypes. For descriptive statistics, mean±standard deviation was used to give continuous data with normal distribution. Median with minimum-maximum values was applied for continuous variables without normal distribution. Numbers and percentages were used for categorical variables. The Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson-Darling tests analyzed the normal distribution of the numerical variables. The independent samples t-test compared two independent groups where numerical variables had a normal distribution. The Mann–Whitney U-test was applied for the variables without normal distribution in comparing two independent groups. The Pearson Chi-square and Fisher's exact tests were used to compare the differences between categorical variables in 2×2 tables. The Kaplan–Meier survival analysis was performed to generate the survival curves. We analyzed the differences between the curves using the log-rank test. The univariate and multivariate logistic regression analyses were performed to analyze the factors that impact the length of overall survival in the groups. Statistically significant factors in the univariate analysis were included in the multivariate analysis. For statistical analysis, Statistical Product and Service Solutions (version 16.0 software for Windows) (Inc., Chicago, IL, USA) was used. The significance level (p-value) was determined at 0.05 in all statistical analyses.

RESULTS

There were 834 (44.2%), 996 (52.8%), and 57 patients (3.0%) in Groups A, S, and AS. There were significant differences in the demographic and tumoral characteristics of the groups ($p<0.05$) (Table 1). In Group S, the proportion of male patients was significantly higher compared to the other groups ($p=0.001$).

Lobectomy was the most frequent resection performed in 74%, 71%, and 63% of the cases in Groups A, S, and

Table 1. Demographic and tumoral characteristics of the study groups

	Group A (n=834)	Group S (n=996)	Group AS (n=57)	p-value
Age (year)†	57.28±8.7	59.24±9.4	57.84±8.6	0.786
Sex‡				
Female	93 (11.2)	24 (2.4)	4 (7)	<0.001
Male	741 (88.8)	972 (97.6)	53 (93)	
Diameter (cm)†	5.29±2.80	5.03±2.23	5.96±2.12	0.001
T stage‡				
1	146 (17.5)	60 (6)	2 (3.5)	<0.001
2	407 (48.8)	592 (59.4)	27 (47.4)	
3	240 (28.8)	258 (25.9)	19 (33.3)	
4	41 (4.9)	86 (8.6)	9 (15.8)	
N stage‡				
0	460 (53)	478 (47.7)	24 (44.4)	<0.001
1	267 (30.8)	398 (39.7)	26 (48.1)	
2	141 (16.2)	126 (12.6)	4 (7.4)	
M stage‡				
0	797 (95.6)	982 (98.6)	55 (96.5)	<0.001
1	37 (4.4)	14 (1.4)	2 (3.5)	
TNM stage‡				
1	241 (28.9)	288 (29)	11 (19.3)	0.001
2	283 (34)	388 (39)	17 (29.8)	
3A	217 (26.1)	209 (21)	18 (31.6)	
3B	67 (8)	99 (10)	9 (15.8)	
4	25 (3)	10 (1)	2 (3.5)	

†Mean±standard deviation, ‡n (%).

Table 3. The rates of 5-year survival in the groups

	Group A (n=834)	Group S (n=996)	Group AS (n=57)	p-value
5-year survival‡	793 (41)	949 (47)	16 (36)	0.001

‡n (%)

Table 4. Univariate and multivariate analysis of the demographic and clinical factors on the overall survival

Factor	Univariate analysis	Multivariate analysis
Age (<60 years vs. ≥60 years)	0.040	0.200
Sex (male vs. female)	0.234	0.686
Diameter (> 5 cm vs. ≥5 cm)	0.030	0.010
T stage (T1-2 vs. T3-4)	0.010	0.090
N stage (N0-N1-N2)	0.010	0.010
M stage (M0 vs. M1)	0.010	0.345
TNM stage (Stages 1–2 vs. Stages 3–4)	0.010	0.010
Histology (squamous-adenocarcinoma-adenosquamous carcinoma)	0.010	0.010
Type of resection (lobectomy vs. pneumonectomy)	0.020	0.432
Positive surgical borders (No vs. yes)	0.010	0.010

AS (Table 2). We detected no significant differences in the outcomes between the study groups (p>0.05) (Table 2). We detected post-operative complications in 18% of all patients (n=339). Although the complication rate in Group AS was higher than in Groups A and S, the difference was insignificant (p=0.453). The types of complications in descending order were as follows: Atrial fibrillation, atelectasis, pneumonia, prolonged air leakage, chylothorax, wound infection, and renal failure.

There was 85 in-hospital mortality (4.5%) in all patients. The mortality rates in the groups were similar (p=0.555). The most frequent deaths were pneumonia, bronchopleural fistula, respiratory insufficiency secondary to acute respiratory distress syndrome, and myocardial infarction.

The 5-year survival rates were 41%, 47%, and 36% in Groups A, S, and AS (p<0.001) (Table 3). The rate of 5-year survival in Group AS was significantly lower than in Groups A and S (p=0.04 and p=0.001). The patients in Group S had a significantly higher rate of 5-year survival than those in Group A (p=0.001).

The univariate and multivariate regression analyses of the demographic and clinical factors on the overall survival are summarized in Table 4. Diameter, N stage, TNM stage, his-

Table 2. Comparison of the treatment details and the outcomes in the study groups

	Group A (n=834)	Group S (n=996)	Group AS (n=57)	p-value
Type of surgery‡				
Lobectomy	617 (73.4)	707 (71)	36 (63.2)	<0.001
Pneumonectomy	175 (20.8)	279 (28)	18 (31.6)	
Segmentectomy/wedge resection	49 (5.8)	10 (1)	3 (5.3)	
Positive surgical borders‡	48 (5.8)	55 (5.5)	7 (12.3)	0.105
Complications‡	158 (18.9)	169 (17)	12 (21.1)	0.453
In-hospital mortality‡	42 (5)	40 (4)	3 (5.3)	0.555

‡n (%).

tology, and positive surgical borders were the independent risk factors for the 5-year survival ($p<0.05$).

DISCUSSION

The findings of this study showed that the histology of NSCLC is an essential clinical parameter affecting the 5-year survival of the patients. The patients with adenosquamous pathology lived shorter than those with squamous and adenocarcinoma histology. We also detected higher 5-year survival rates in patients with squamous histology than in those with adenocarcinoma.

The impact of histology on the rates of non-local failures and overall survival has been debated in the previous studies. Several authors reported that the histology of NSCLC has no impact on the prognosis of the disease.[11,15,17,18] However, several authors found that squamous histology was significantly associated with the increased risks of local, regional, and distant failure and death compared to adenocarcinoma histology.[11,14,15,19] Rabinel et al.[19] showed that squamous histology was an independent risk factor for microscopic residual disease due to incomplete resection. They thought that tumoral characteristics of squamous histology, like the more central location and large tumor with lymph node involvement, are the significant issues related to poor outcomes.[19] Shin et al.[3] found that adenocarcinoma was significantly associated with higher overall survival in patients with NSCLC. Sayan et al.[2] found that the histopathological subtypes other than squamous cell carcinoma and adenocarcinoma were poor prognostic factors. They included pleomorphic adenocarcinoma, adenosquamous carcinoma, and large cell carcinoma in the subgroup of other histologic types.

Contrary to these findings, several studies reported improved survival in patients with squamous carcinoma compared with adenocarcinoma after pneumonectomy or stereotactic body radiation therapy.[4,20] In the present study, the 5-year survival rate was the worst in adenosquamous carcinoma and the best in squamous cell carcinoma. This cohort had considerable differences in patient and disease-related characteristics, including demographic data, TNM stages, and surgical and adjuvant treatment modalities. Besides, there has been a significant improvement in the treatment of adenocarcinoma using the targeted therapies in the recent decades after 2000.[1,19] Hence, we believe that heterogeneity in the patient- and disease-related characteristics and the changes in treatment modalities might be the underlying reasons for these controversies. We also believe that as the duration of the follow-up increases, the chance of detecting significant differences regarding the association between prognosis and histology might be more precise.[13] Hence, larger cohorts with long-term survival and outcome analyses should be conducted to evaluate the prognostic impact of adenosquamous histology of NSCLC.

Nevertheless, all these studies usually grouped NSCLC into two main groups; squamous cell carcinoma and adenocarcinoma histology types. The other histologic types were included in the same name as "mixed/others/not otherwise specified."[3,4,6,9,11,19–25] Therefore, these studies have not analyzed the specific subgrouping of adenosquamous histology and its impact on survival. Several studies reported that the rate of adenosquamous histology ranged from 1.8% to 3.5%.[5,15,23] In the literature, a limited number of studies focused on adenosquamous carcinoma. Wang et al.[12] evaluated the clinicopathological characteristics and prognosis of resectable lung adenosquamous carcinoma. The incidence of adenosquamous carcinoma in their population-based cohort was 2.5%. They found that higher pleural invasion and poorer differentiation were more frequently detected in adenosquamous cancer patients than those with adenocarcinoma and squamous cell carcinoma. A worse survival in these patients was the consequence. Similar findings have been reported by the others.[26] We also found similar results in our study. The rate of positive surgical borders was higher in Group AS, reflecting aggressive behavior. Based on these findings, we may conclude that adenosquamous carcinoma is associated with poor outcomes in patients with NSCLC.

The applicability of an appropriate surgical treatment is another critical factor.[27] The previous studies reported that pneumonectomy or complex segmentectomy was significantly associated with better overall survival in NSCLC patients.[6,7,22] In these studies, the authors found no significant differences in the proportion of histological subgroups between different operative groups. Contrary to these findings, others showed similar overall survival rates in patients who underwent segmentectomy, lobectomy, or wedge resection for NSCLS.[8,9,21,22,27] In Raman's study,[5] in which the 2004–2015 National Cancer Database was used, the authors reported that lobectomy was superior to segmentectomy regarding the overall survival in patients with adenocarcinoma with a tumor size of 10 mm and squamous carcinoma with a tumor size of 15 mm. Pneumonectomy has been questioned considering its higher post-operative morbidity and mortality risk. It has been offered cautiously over the past decades.[6,28] Saji et al.[22] recently reported that segmentectomy should be the standard surgical procedure for small peripheral NSCLC. In our cohort, lobectomy was the most frequent type of surgery in three groups similar to the others.[29] In Dantas's study,[29] the overall survival in the 5th year was superior for lobectomy compared with limited resections (segmentectomy or wedge resection). However, we could not evaluate the impact of different tumoral characteristics and surgical modalities on overall survival. Hence, more extensive cohort studies with propensity-matched analysis are needed to investigate the effect of different surgical modalities on the survival of NSCLC.

Other vital clinical parameters, including age, time to surgery, and extent of the surgical resection, are related to the survival and other prognostic outcomes in patients with NSCLC.[21,30] Baine et al.[14] reported that advancing age and medical inoperability affect the local, regional, and

distant control. They thought that advanced age leading to a relatively immunocompromised situation might be a factor that negatively impacted the prognostic parameters in these patients. We did not detect a significant difference in the demographic data of the groups. Although significant differences were seen in the groups' tumor- and treatment-related characteristics, we did not perform a subgroup analysis in this retrospective study.

The retrospective design of this single-center study was the major limitation. Due to the study's retrospective design, we could not gather information about cigarette usage, cardiac or pulmonary function, laboratory testing, and usage and sequence of medical and surgical treatment modalities. This issue might lead to a selection bias because of the uncontrolled, potentially confounding variables.

CONCLUSION

The tumor histology of NSCLC was a significant factor in patient outcomes. Patients with squamous histology fare better than those with adenosquamous and adenocarcinoma histological types. Adenosquamous histology was the worst type of NSCLC regarding the patient outcomes.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.D.; Design: S.D.; Supervision: S.D.; Fundings: S.D.; Materials: M.B.; Data: M.B.; Analysis: M.B., S.D.; Literature search: M.B., S.D.; Writing: M.B., S.D.; Critical revision: M.B., S.D.

Conflict of Interest

None declared.

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Küçük Hücreli Dışı Akciğer Kanserinin Histolojik Alt Tipleri ile Sağkalım Arasındaki İlişki: 1887 Hastanın Geriye Dönük Kohort Analizi

Amaç: Küçük hücreli dışı akciğer kanserinin histolojik alt tipleri hastalığın sonucu ile ilişkili olabilir. Nadir fakat agresif bir tümör olan adenoskuamöz karsinom, zayıf sağkalım oranları ile ilişkilendirilmiştir. Bu çalışmada küçük hücreli dışı akciğer kanserinin histolojik alt tiplerine sahip hastaların cerrahi tedavi sonrası sağ kalım oranlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2000–2009 yılları arasında küçük hücreli dışı akciğer kanserli hastalarda cerrahi tedavi uygulanan tek merkezli geriye dönük bir çalışma yapılmıştır. Histolojik tipler adenokarsinom (Grup A), skuamöz hücreli (Grup S) ve adenoskuamöz karsinom (Grup AS) olarak gruplandırılmıştır. Hastaların demografik ve klinik özellikleri ile sağkalım verileri toplandı. Birincil sonuç, ameliyat sonrası beş yıl hayatta kalan hastaların oranıydı.

Bulgular: Toplam 1887 hasta (Grup A: 834 (%44.2), Grup S: 996 (%52.8) ve Grup AS: 57 hasta (%3.0) dahil edildi. Grup A, S ve AS'deki olguların %74'ünde, %71'inde ve %63'ünde lobektomi en sık uygulanan rezeksiyondu. Gruplarda hastane içi ölüm oranları benzerdi (p=0.555). A, S ve AS gruplarında beş yıllık sağkalım oranları %41, %47 ve %36 idi. Grup AS'de beş yıllık sağkalım oranı Grup A'ya (p=0.04) ve Grup S'ye (p=0.001) göre anlamlı derecede düşüktü. Grup S, Grup A'ya göre anlamlı olarak daha yüksek beş yıllık sağ kalım oranına sahipti (p=0.001).

Sonuç: Adenoskuamöz histoloji, sağkalım sonuçları açısından küçük hücreli dışı akciğer kanserinin en kötü tipiydi. Skuamöz histolojiye sahip hastalar, adenoskuamöz ve adenokarsinom histolojik alt tipleri olanlardan daha iyi sonlanıma sahiptir.

Anahtar Sözcükler: Adenokarsinom; adenoskuamöz karsinom; cerrahi; küçük hücreli dışı akciğer kanseri; sağkalım; skuamöz hücreli karsinom.