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Survival in adenosquamous cancer of the lung: is it really so unfavorable?

Akciğerin adenoskuamöz kanserinde sağkalım: Gerçekten o kadar kötü mü?

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ABSTRACT

Background: This single-center study aims to investigate whether a significant difference exits between the survival rates of patients operated for adenosquamous cancer of the lung (ASCL) and patients operated for adenocarcinoma or squamous cell carcinoma.

Methods: A total of 2,203 patients (1,977 males, 226 females; mean age 57.8±34.9 years; range 22 to 86 years) operated for non-small cell lung cancer in our hospital between January 2002 and January 2011 were retrospectively analyzed for pathological diagnosis, survival, and tumor staging.

Results: As a result of pathological analysis, the diagnosis of adenosquamous cancer was confirmed in 46 out of 2,203 (2.1%) patients. The median survival time was 53.6 months (range 21.1 to 68.2 months) for adenocarcinoma, 48.1 months (range 24.4 to 66.9 months) for squamous cell cancer, and 27.9 months (range 10.7 to 44.6 months) for ASCL (p=0.026). The median survival time was 21.6 months in the group of patients with predominating adenocarcinoma, 21.4 months in the group of patients with predominating squamous cell carcinoma, and 37.8 months in the group of patients with codominant cell lines (p=0.007).

Conclusion: In our study, the survival rate of ASCL patients was lower than that of patients with squamous cell carcinoma or adenocarcinoma. Further clinical studies are needed to investigate whether adjuvant chemoradiotherapy following surgical resection improves overall survival rates.

Keywords: Adenosquamous cancer; lung cancer; surgical resection; survival time.

ÖZ

Amaç: Bu tek merkezli çalışmada, akciğer adenoskuamöz kanseri (AAK) nedeni ile ameliyat edilmiş hastaların sağkalım oranları ile adenokarsinom veya skuamöz hücreli karsinom nedeni ile ameliyat edilmiş hastaların sağkalım oranları arasında anlamlı bir farklılık olup olmadığı araştırıldı.

Çalışma planı: Ocak 2002 - Ocak 2011 tarihleri arasında hastanemizde küçük hücreli dışı akciğer kanseri nedeni ile ameliyat edilen toplam 2203 hasta (1977 erkek, 226 kadın; ort. yaş 57.8±34.9 yıl; dağılım 22-86 yıl) patolojik tanı, sağkalım ve tümör evresi yönünden retrospektif olarak analiz edildi.

Bulgular: Patolojik analiz sonucunda, 2203 hastanın 46'sında (%2.1) adenoskuamöz kanser tanısı doğrulandı. Ortanca sağkalım süresi adenokarsinom için 53.6 ay (dağılım 21.1-68.2 ay), skuamöz hücreli karsinom için 48.1 ay (dağılım 24.4-66.9 ay) ve AAK için 27.9 ay idi (dağılım 10.7-44.6 ay) (p=0.026). Ortanca sağkalım süresi adenokarsinom predominansı olan hasta grubunda 21.6 ay, skuamöz hücreli karsinom predominansı olan hasta grubunda 21.4 ay, kodominant hücre dizisi olan hasta grubunda 37.8 ay idi (p=0.007).

Sonuç: Çalışmamızda, AAK hastalarının sağkalım oranı skuamöz hücreli karsinom veya adenokarsinom hastalarınınkinden daha düşük idi. Cerrahi rezeksiyon sonrası adjuvan kemoradyoterapinin genel sağkalım oranlarını iyileştirip iyileştirmediğini araştıracak ileri klinik çalışmalar gereklidir.

Anahtar sözcükler: Adenoskuamöz karsinom; akciğer kanseri; cerrahi rezeksiyon; sağkalım süresi.

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Adenosquamous cancer of the lung (ASCL) is a rarely encountered malignancy. Its rate of occurrence was reported between 1.5 and 4.5% in various surgical series in the literature.[1-6] According to the World Health Organization (WHO) classification declared in 2004, the adenocarcinoma and squamous cell carcinoma (SCC) components may be named as adenosquamous cancer if each type represents more than 10% of the tumor itself.[7]

There are several clinical reports suggesting that both components of ASCL possess similar biological features and behavioral characteristics,[8,9] while various reports indicate that the survival in ASCL is much worse than adenocarcinoma and SCC, with a five-years cumulative survival rate between 0 and 25%.[1-6] Despite the available reports on ASCL in the literature, the survival and prognosis in this malignancy still remain largely undetermined.

In this single-center study, we aimed to investigate whether a significant difference exits between the survival rates of patients operated for ASCL and patients operated for adenocarcinoma or SCC.

PATIENTS AND METHODS

A total of 2,203 patients (1,977 males, 226 females; mean age 57.8±34.9 years; range 22 to 86 years) operated for non-small cell lung cancer Süreyyapaşa Chest Disease and Thoracic Surgery Training and Research Hospital, between January 2002 and January 2011 were recruited and data were retrospectively analyzed for the pathological diagnosis, survival, and tumor staging.

Standard diagnostic workup for each patient included plain chest X-ray, thoracic computed tomography (CT), abdominal CT, and cranial magnetic resonance imaging until 2007; thereafter, positron emission tomography (PET)-CT replaced abdominal CT. Fiberoptic bronchoscopy was performed in all patients, combined with transthoracic fine-needle aspiration biopsy in selected cases. Until PET-CT became available for diagnostic and staging procedures, all of the patients underwent preoperative standard cervical mediastinoscopy. Thereafter, preoperative mediastinoscopy was only performed in those patients with a mediastinal lymphadenopathy greater than 1 cm in diameter radiologically, and/or carrying a high suspicion for malignancy. Patients who underwent R_0 (resection with no residual macroscopic or microscopic tumor) resection were included and systematic lymphadenectomy was performed in all of these subjects. All patients except with stage 1 disease received adjuvant chemotherapy in the postoperative period. Radiotheraphy was added to the treatment of patients with postoperative N_2 disease.

Patients were followed-up every three months in the first year and every six months thereafter. The follow-ups lasted until 2013 and the Turkish Republic Civil Registry Office database was utilized for patients who did not come to the outpatient clinic.

The seventh staging system announced in 2009 by International Association for the Study of Lung Cancer was applied for the pathological staging,[10] while histopathological type was identified according to the recommendations of the WHO in 2004.[7]

Statistical analysis

Statistical Package for the Social Sciences for Windows version 15.0 software program (SPSS Inc., Chicago, IL, USA) was utilized for the statistical analysis. Kaplan-Meier test was performed for the survival analysis and Wilcoxon log-rank test for the comparison of the study groups. Maximum type 1 error was accepted as 0.05 and a p value of <0.05 was considered to be statistically significant. The distribution of data was addressed with a confidence interval (CI) of 95%.

RESULTS

Following the pathological examination, the diagnosis of adenosquamous cancer was confirmed in 46 out of 2,203 (2.1%) patients. Other types of cancer detected in the study consisted of SCC in 1,174 patients (53.3%), adenocarcinoma in 869 patients (39.4%), large cell carcinoma in 57 patients (2.6%), small cell carcinoma in 31 patients (1.4%), and mucoepidermoid carcinoma in 26 patients (1.2%). The demographic characteristics of the cohort groups were summarized in Table 1.

The groups demonstrated a homogenous distribution in regard to sex and tumor stages (p=0.102 and p=0.089, respectively). Of the patients, 41.5% operated for adenocarcinoma had stage 1 disease, whereas this ratio was 18% and 24% for patients operated for SCC and ASLC, respectively. The median survival time was 53.6 months (95% CI, 21.1 to 68.2) for adenocarcinoma patients, 48.1 months (95% CI, 24.4 to 66.9) for SCC patients, and 27.9 months (95% CI, 10.7 to 44.6) for ASCL patients, revealing a statistically significant difference in survival among these groups (p=0.026). The Wilcoxon, Gehan-Breslow statistical analysis revealed that this finding was a direct result of the survival difference between patients with stage 1 and stage 2 diseases.

Table 1. Comparison of demographical distribution, stage, and survival characteristics between groups

	Squamous cell carcinoma (n=1174)		Adenocarcinoma (n=869)		Adenosquamous carcinoma (n=46)		
	n	%	n	%	n	%	*p*
Gender							
Female	104		98		4		0.102
Male	1070		771		42		
Stage							
1	211	18.0	361	41.5	11	23.9	0.089
2	785	66.9	394	45.4	29	63.1	
3A	178	15.1	114	13.1	6	13.0	
Median survival (months)		48.1		53.6		27.9	0.026

The analysis of survival rates according to the various stages of different histopathologies demonstrated a significant difference between patients with stage 1 (p=0.026) and stage 2 (p=0.041) adenocarcinoma, SCC, and ASCL. The survival rate of stage 3A disease was similar in all groups (p=0.109) (Table 2).

The histopathological subtype analysis of the cases diagnosed with adenosquamous cancer revealed 18 patients with predominating adenocarcinoma (39%), 12 cases with predominating SCC (26%), and 16 patients exhibiting balance in these cell lines. The median overall survival time was recorded as 21.6 months (95% CI, 17.7 to 24.1) in the group of patients with predominating adenocarcinoma, 21.4 (95% CI, 16.9 to 26.6) months in the group of patients with predominating SCC, and 37.8 (95% CI, 29.7 to 44.8) months in the group of patients with codominant cell lines (p=0.007).

DISCUSSION

Adenosquamous cancer of the lung is a rarely encountered sub-type of lung cancer. Its rate of occurrence was reported between 1.5 and 4.5% in various surgical series in the literature.[1-6] By definition, the adenocarcinoma and SCC components each represent at least 10% of the tumor itself. In our series, the prevalence of ASCL among operated patients with all types of lung cancer was recorded as 2.1%.

There are several reports in the literature indicating that the postoperative survival of patients with ASCL does not differ significantly from patients with other types of lung cancer.[4,11] Nevertheless, it is generally accepted that this specific subtype is worse than others in terms of postoperative prognosis and survival. A study by Naruke et al.[12] supporting this approach revealed a five-year survival rate of 36.7% following surgical intervention in patients with small cell carcinoma of the lung and 18.9% in patients with ASCL. In the same study, the tumor node metastasis staging was also reported to be higher in ASCL patients. Studies conducted on this topic mostly suffer from the limited availability of patient series and the uncertainty of data on the characteristics

Table 2. Stage-dependent survival rates in each group

	Histopathological type	Survival time (months)	95% CI	
		Mean±SD	Min.-Max.	*p*
Stage 1	Adenocarcinoma	58.7±9.8	49.1-68.4	0.026
	Squamous cell carcinoma	57.2±9.3	46.3-66.9	
	Adenosquamous cancer	40.8±7.9	31.9-52.3	
Stage 2	Adenocarcinoma	41.2±7.2	29.8-50.0	0.041
	Squamous cell carcinoma	39.5±6.1	28.1-49.9	
	Adenosquamous cancer	29.0±5.6	19.1-36.6	
Stage 3A	Adenocarcinoma	29.6±7.8	14.3-39.9	0.109
	Squamous cell carcinoma	32.4±8.4	23.6-41.2	
	Adenosquamous cancer	23.8±7.3	11.4-29.8	

SD: Standard deviation; Min.: Minimum; Max.: Maximum; CI: Confidence interval.

and prognosis of the tumor. Our study has also demonstrated a similar result and the survival rate of ASCL patients was lower than that of patients diagnosed with adenocarcinoma and SCC.

In a study with 2,160 patients who have undergone resection for primary lung carcinoma, 56 patients (2.6%) were diagnosed with ASCL and among the patients with stage 1 and 2 disease the ASCL survival rate was lower than that of adenocarcinoma and SCC.[13] In a similar study by Cooke et al.,[14] the overall survival rates of ASCL and SCC were lower than that of adenocarcinoma. The five-year survival rate for stage 1 tumors was reported as 62.0% for ASCL, 69.2% for SCC, and 73.2% for adenocarcinoma. The survival analysis in our study demonstrated a striking difference between adenocarcinoma, SCC and ASCL, among patients with stage 1 and stage 2 tumors. Although the adenocarcinoma survival rate was higher in stage 3A tumors, the difference between the study groups was not statistically significant (p=0.109).

One of the largest studies on ASCL was conducted by Gawrychowski et al.[1] with 96 patients. In this study, the comparison of five-year survival among stage 1A patients revealed no significant difference between adenocarcinoma and ASCL. Nevertheless, the survival rate of ASCL was significantly lower in other stages.

The main reason for the significantly lower survival rate in stage 1 and 2 ASCL patients is the relatively more aggressive behavior of the tumor in comparison to the squamous cell and adenocarcinoma subtypes. In stage 3A, the survival clearly drops in all patient groups.[2]

Owing to the rapid spread of the tumor in ASCL patients, the diagnosis usually takes place at an advanced stage. In our study, only 24% of the patients with an operable ASCL were diagnosed on stage 1. The difficulty of diagnosis at an early stage and the relatively higher rate of administration of adjuvant chemoradiotherapy were held responsible for the difference in survival of these patients.[15]

It is still indefinite why ASCL tends to behave more aggressively than other types of lung cancer. Due to the heterogenic nature of the tumor, the identification of pathological features is difficult. Several authors have reported that the behavioral pattern of ASCL resembles adenocarcinoma more than SCC.[16] Various other reports have suggested a similarity in behavioral pattern and biological features of both ASCL components.[8,9]

A study with multivariate analysis demonstrated better survival in the presence of a balance between both components of ASCL; the loss of balance was noted as the main reason for lower survival.[1] Similar to various other studies in the literature, the survival of ASCL patients with balanced histopathological features in our study were better than the survival of patients with predominating adenocarcinoma or SCC component. The reason for this significant difference is not clear. Nevertheless, according to this finding, adjuvant chemoradiotherapy might be regarded as a treatment choice even for stage 1 patients, if a histopathological predominance of either adenocarcinoma or SCC is detected.

The first limitation of our study was that patients with stage 1 tumors did not receive adjuvant therapy; thus the survival analysis does not cover the influence of a possible adjuvant therapy on patients. Another limitation was related to the fact that stage 3A comprises a rather heterogeneous group of tumors. The prevalence of ASCL is already quite low, thus stage 3A ASCL cases are very rarely encountered. This restriction also interferes with the application of a statistically convincing comparison of subgroups in stage 3A tumors.

In conclusion, the prognosis of ASCL was shown to be worse than SCC and adenocarcinoma, in accordance with various reports in the literature. This finding was especially pronounced in patients with stage 1 and stage 2 tumors. In these patient groups, new clinical studies are needed to investigate whether adjuvant chemoradiotherapy following surgical resection improves overall survival rates.

Declaration of conflicting interests

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