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Does endobronchial lesion affect the lymph node status in non-small cell lung cancer?

Küçük hücreli dışı akciğer kanserinde endobronşiyal lezyon lenf nodu durumunu etkiler mi?

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ABSTRACT

Background: This study aims to evaluate whether or not there is a relationship between endobronchial lesion and hilar and/or mediastinal lymph node metastasis in non-small cell lung cancer.

Methods: A total of 687 patients (636 males, 51 females; mean age 60.8±9.1 years; range 29 to 82 years) who were performed anatomical resection with the diagnosis of non-small cell lung cancer between January 2005 and December 2011 were analyzed retrospectively. Patients with or without bronchoscopically detected endobronchial lesion were divided into two groups. The two groups were compared in terms of having or not having hilar or ipsilateral mediastinal lymph node metastasis.

Results: As a result of an evaluation with chi-square analysis performed on patient groups with (n=174) or without (n=513) endobronchial lesion, we detected a significant correlation between the presence of endobronchial lesion and hilar lymph node metastasis status (p=0.014), while we did not detect a significant correlation between the presence of endobronchial lesion and ipsilateral mediastinal lymph node metastasis status (p=0.383). Five-year survival in patients with or without endobronchial lesion was 58.6% and 40.2%, respectively, with a statistically significant correlation (p<0.001).

Conclusion: Hilar lymph node metastasis is significantly more frequently observed in non-small lung cancer cases with endobronchial lesion. This fact raises the suspicion that metastasis may develop via the peribronchial lymphatics.

Keywords: Endobronchial lesion; lung cancer; lymph node metastasis.

ÖZ

Amaç: Bu çalışmada küçük hücreli dışı akciğer kanserinde endobronşiyal lezyon ile hiler veya mediastinal lenf nodu metastazı arasında ilişki olup olmadığı değerlendirildi.

Çalışma planı: Ocak 2005 - Aralık 2011 tarihleri arasında küçük hücreli dışı akciğer kanseri tanısı ile anatomik rezeksiyon uygulanmış toplam 687 hasta (636 erkek, 51 kadın; ort. yaş 60.8±9.1 yıl; dağılım 29-82 yıl) retrospektif olarak incelendi. Bronkoskopik olarak saptanmış endobronşiyal lezyonu olan ve olmayan hastalar iki gruba ayrıldı. İki grup, hiler veya aynı taraf mediastinal lenf nodu metastazı olup olmaması yönünden karşılaştırıldı.

Bulgular: Endobronşiyal lezyonu olan (n=174) ve olmayan hasta gruplarında (n=513) ki-kare analizi ile yapılan değerlendirmede endobronşiyal lezyon varlığı ve hiler lenf nodu metastazı durumu arasında anlamlı bir ilişki saptanır iken (p=0.014) endobronşiyal lezyon varlığı ve aynı taraf mediastinal lenf nodu metastazı durumu arasında anlamlı bir ilişki saptanmadı (p=0.383). Endobronşiyal lezyonu olan ve olmayan hastalarda beş yıllık sağkalım sırası ile %58.6 ve %40.2 olup aralarında istatistiksel olarak anlamlı farklılık vardı (p<0.001).

Sonuç: Endobronşiyal lezyonu olan küçük hücreli dışı akciğer kanseri olgularında hiler lenf nodu metastazı anlamlı olarak daha sık görülmektedir. Bu durum peribronşiyal lenfatikler aracılığı ile metastaz gelişebileceği yönünde şüphe uyandırmaktadır.

Anahtar sözcükler: Endobronşiyal lezyon; akciğer kanseri; lenf nodu metastazı.

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Pneumonectomy was started to be used as the surgical treatment in lung cancer firstly by Evarts Graham in 1932.[1] Even though the treatment modalities have changed over the years, one of the most important factors that determine the treatment and prognosis of non-small cell lung cancer (NSCLC) is the presence of hilar and mediastinal lymph node metastasis.[2,3]

Lung cancer is diagnosed in metastatic phases or locally late stages due to its natural course, thus surgical treatment is not an option in 70% of the patients.[4] The stage of the disease is the most important factor of the prognosis and treatment.[5] The tumor, node and metastasis staging system puts forth the spreading of the cancer by evaluating factors such as tumor size and invasion, lymphatic invasion and presence of metastatic disease.[6] Mediastinal lymph node metastasis is one of the most important criteria in determining the prognosis of lung cancer. Therefore, in this study, we aimed to evaluate whether or not there is a relationship between endobronchial lesion (EBL) and hilar and/or mediastinal lymph node metastasis in NSCLC.

PATIENTS AND METHODS

A total of 687 patients (636 males, 51 females; mean age 60.8±9.1 years; range 29 to 82 years) who had undergone anatomical resection with the diagnosis of NSCLC in Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital between January 2005 and December 2011 were analyzed retrospectively. The inclusion criteria for the study were: *(i)* having a pathological diagnosis of NSCLC, *(ii)* being in T_{1a}, T_{1b}, T_{2a}, T_{2b}, T_3 stages pathologically, and *(iii)* having undergone anatomical resection, whereas the exclusion criteria were: *(i)* having a diagnosis of carcinoid tumor, *(ii)* having a satellite nodule in the same lobe, *(iii)* having a nodule in the other lobe, *(iv)* being in T_4 stage, and *(v)* having a diagnosis of small cell lung cancer. The patients were divided into two groups as those with or without bronchoscopically detected EBL. The two groups were compared in terms of having hilar (N_1) or ipsilateral mediastinal (N_2) lymph node metastasis. The study protocol was approved by the Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) software program was used in the analysis of the data. Suitability of the quantitative data for normal distribution was analyzed with Kolmogorov-Smirnov test and parametric methods were used in the analysis of the variables with normal distribution and homogenous variance and non-parametric methods were used for the other variables. Independent t and Mann-Whitney U tests were used to compare independent groups. Partial correlation test was used to analyze the correlations of the variables after the quantitative data were controlled with the main factor. Pearson and chi-square tests were used to compare the categorical data and logistic regression analysis was used to identify the cause and effect relationship between the explanatory variables in dual (diotom) and multiple (multinominal) categories. Kaplan-Meier (product limit method) analysis was used to analyze the effects of factors on mortality and life time and Cox regression analysis was used to measure the effects of the prognostic variables on life time compared to the main factor. The quantitative data were expressed as mean±standard deviation and median±interquartile range values and the categorical data were expressed as number (n) and percentages (%) in the tables. The data were analyzed in a 95% confidence interval and a *p* value less than 0.05 was accepted as significant.

RESULTS

There was no EBL in 513 patients (74.7%) whereas 174 patients (25.3%) had EBL. Of the patients, 174 (25.33%) received neoadjuvant treatment whereas 513 (74.67%) did not. The demographic data of both groups were displayed in Table 1.

Our series included 380 (55.32%) squamous cell carcinomas (SCCs), 238 (34.65%) adenocarcinomas, 50 (7.27%) large cell carcinomas and 19 (2.76%) other non-small cell lung carcinomas. The presence of EBLs in SCC was significantly more frequent ($p<0.001$) compared to adenocarcinoma ($p<0.001$). In the general group, the median survival was 52.1 months in SCC, 51.5 months in adenocarcinoma, and 54.72 months in large cell carcinoma, without a statistically significant difference ($p=0.592$).

Pathological stage distribution of patients revealed that 155 (22.56%) were stage 1A, 134 (19.5%) were stage 1B, 127 (18.49%) were stage 2A, 146 (21.25%) were stage 2B, and 125 (18.2%) were stage 3A. The frequency of EBLs was statistically significantly increased in stage 3A ($p=0.006$).

According to the distribution of lymph node status (N), 491 patients (71.47%) were in N_0, 100 (14.55%) were in N_1, and 96 (13.97%) were in N_2 groups. There was a significant increase in the frequency of pathological N_1 in the presence of EBL ($p=0.014$), whereas no such

Table 1. Characteristics of patients with or without endobronchial lesions

	EBL (-) (n=513)			EBL (+) (n=174)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			61.2±9.2			59.7±8.9	0.062
Gender							
Male	467	91		169	97.1		0.460
Female	46	9		5	2.9		0.011
Neoadjuvant therapy							
Neoadjuvant (-)	440	85.8		142	81.6		0.617
Neoadjuvant (+)	73	14.2		32	18.4		0.222
Histopathological subtype							
Squamous cell carcinoma	231	45		149	85.6		<0.001
Adenocarcinoma	221	43.5		17	9.8		<0.001
Large cell carcinoma	43	8.4		7	4		0.066
Other NSCLC	18	3.5		1	0.6		0.045
Operation type							
Lobectomy	445	86.7		125	71.8		0.064
Pneumonectomy	68	13.3		49	28.2		<0.001
N status							
N_0	381	74.3		110	63.2		0.140
N_1	64	12.5		36	20.7		0.014
N_2	68	13.2		28	16.1		0.383
Stage							
1A	124	24.2		31	17.8		0.129
1B	107	20.9		27	15.5		0.170
2A	93	18.1		34	19.5		0.703
2B	109	21.2		37	21.3		0.991
3A	80	15.6		45	25.9		0.006

EBL: Endobronchial lesion; SD: Standard deviation; NSCLC: Non-small cell lung cancer; N: Lymph node.

correlation was detected for N_2 (p=0.383). When the survival in general group of patients was evaluated by taking the N factor into account, median survival time was 58.8 months in N_0, 49.2 months in N1, and 39.7 months in N_2 groups (Table 2). The survival time was statistically significantly better in the presence of EBLs in N_0 and N_1 groups (p=0.007). The survival median was better in the presence of EBLs in N_2 group, without any statistical significance.

The anatomical resections performed on the patients were divided into two groups as lobectomy and pneumonectomy. There were 117 patients (17.03%) in the pneumonectomy group and 570 patients (82.97%) in the lobectomy group. The frequency of pneumonectomy was significantly increased in patients with EBLs (p<0.001).

Five-year survival rate in the general group was 45.6%. Median life time was 55.5 months in general;

Table 2. Five-year survival analyses of lymph node status

	Overall 5 year survival rate	EBL (5 year survival rate)		
		EBL (-)	EBL (+)	
	%	%	%	*p*
All group	45.6	40.2	58.6	<0.001
N status				
N_0	49.9	45.2	62.1	0.007
N_1	39.1	25.2	62.6	0.007
N_2	26.1	21	38.5	0.183

EBL: Endobronchial lesion; N: Lymph node.

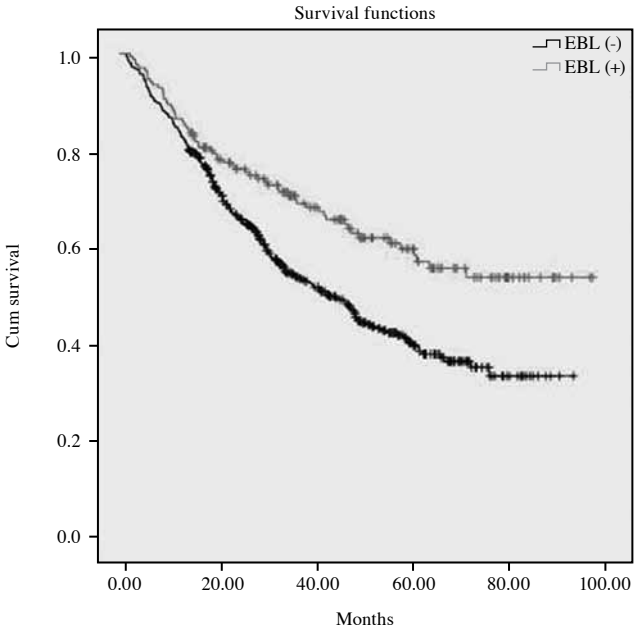

Figure 1. Study group survival.
EBL: Endobronchial lesion.

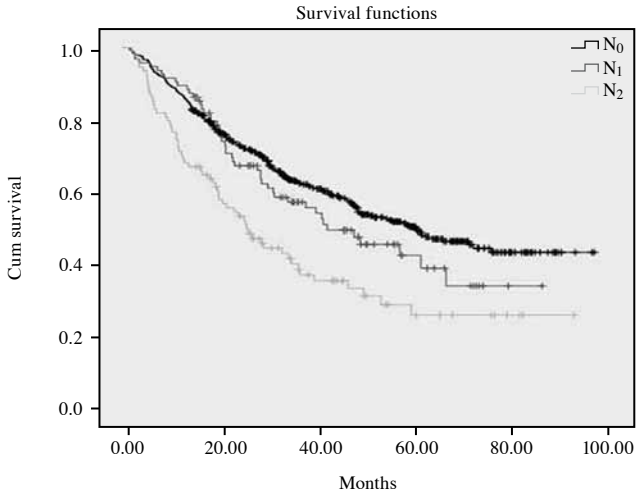

Figure 2. Lymph node status versus survival.
N: Lymph node; N_0: No lymph node metastasis; N_1: Hilar lymph node metastasis; N_2: Ipsilateral mediastinal lymph node metastasis.

50.4 months in patients without EBL and 65.4 months in patients with EBL. The five-year survival was 40.2% in patients without EBL and 58.6% in patients with EBL. The difference in survival rates between both groups was statistically significant ($p<0.001$).

DISCUSSION

In the literature, the effect of the localization of the tumor on survival was investigated as well as the lymph node metastasis in treatment efficacy.[7,8] However, to our knowledge, there is no study concerning the relationship between the presence of EBL and lymph node metastasis and its effect on survival, which is our hypothesis subject; we detected in the literature only a few studies that are close to our perspective indirectly.[9,10] Ito et al.[10] evaluated a tumor that was related to the extrapulmonary bronchus or localized in the extrapulmonary bronchus as central type and other tumors that did not meet these criteria as peripheral type. Ketchedjian et al.[7] performed bronchoscopy preoperatively rather than thorax computed tomography to determine the tumor localization as central or peripheral as we also did in our study. The tumor that could be seen bronchoscopically or inside one third of the lung area was determined as central while the others were determined as peripheral.[7] In our study, the term peripheral tumor was used if there was no EBL detected bronchoscopically and the term central tumor was used if any EBL was detected. Central tumors were also identified as tumors that could be observed directly bronchoscopically.

In previous studies, other controversial issues included tumor localizations that metastasized to the lymph nodes more, and whether or not these metastases' were more hilar or mediastinally located. Ito et al.[10] reported that even though lymph node metastasis was seen more in peripheral tumors, there was no statistically significant difference from the central tumors ($p=0.124$). On the other hand, Krdzalic et al.[8] stated that N_1 metastasis was significantly more frequent in central tumors. Furthermore, Marra et al.[11] analyzed 535 patients with N1 metastasis and observed that N_1 metastasis was more frequent in central tumors ($p<0.001$). These findings support our study. Moreover, Graham et al.[9] showed that lymph node metastasis rate increased as the tumors moved from peripheral to central areas. As the localization of the tumor distanced from peripheral, segmental, bronchial, or lobar bronchial to main bronchial, the rate of lymph node metastasis was found to be 27%, 42%, 68% and 73%, respectively, and statistically significant.[9] In this study, it was demonstrated that in central tumors, both N_1 and N_2 metastases were significantly more frequent.[9] In our study, we determined that both N_1 and N_2 metastases were increased in tumors with EBLs. The increase in N_1 metastasis was statistically significant, whereas the increase in N_2 metastasis was not. These results support our hypothesis that the tumor may metastasize more frequently to the hilar regional lymph nodes via the peribronchial lymphatics in the presence of EBL.

Another important aim of our study was to analyze the difference between prognosis and survival in peripherally and centrally located tumors. Ketchedjian et al.[7] showed that the median survival in central and peripheral tumors was 18 and 39 months, respectively, with a statistically significant difference. In another study, five-year survival rate in central and peripheral tumors was 38% and 45%, respectively, with no statistically significant difference.[11] In addition, Ito et al.[10] found that the five-year survival rates were better in central tumors compared to peripheral tumors. In this study, five-year survival in central and peripheral tumors was 51.5% and 21.2%, respectively, with a statistically significant difference in favor of central tumors (p=0.034). Our findings support the results of this study. When general survival and N were compared in our study, survival was better in the presence of EBLs.

As known, adenocarcinomas tend to be more peripherally whereas SCCs tend to be more centrally located.[12] A study performed by Uslu et al.[13] supported this. Squamous cell carcinoma is seen more in the bronchoscopically detected vegetating lesions or tumoral infiltrations.[13] In their study, Watanabe et al.[14] showed that the majority of the histological types of peripheral tumors were adenocarcinomas. In a study by Brooks et al.,[15] the frequency of SCCs was found to be increasing in central tumors. In our study, SCC was seen more than adenocarcinoma in endobronchial tumors (85.6% vs. 9.8%) and the difference in between was statistically significant. In peripheral tumors, adenocarcinoma incidence was 37.4% and SCC incidence was 45%, and although not statistically significant, there was a dominance of SCC.[16] According to the literature, adenocarcinoma incidence is higher in females.[17] We detected that the incidence of EBL was significantly lower in females.

Another condition that may affect survival is tumor type. A great number of studies have demonstrated that the survival of patients with SCCs is better than those with adenocarcinomas. Similarly, Carbone et al.[16] detected that five-year survival probability in SCCs was better than adenocarcinomas (48.8% and 40.9%, respectively). Also, in another study, five-year survival in SCC was better than adenocarcinoma.[19] However, a review of the literature revealed that the effect of histological type on survival is still controversial.[18] Considering our overall patient population, the five-year survival of patients with SCCs was 38.6%, whereas it was 33.6% in those with adenocarcinomas, with no statistically significant difference. In our study, there was a significant difference between the presence and absence of EBL in terms of survival. For this reason, even though SCC was seen more in patients with EBLs, we think that the difference between the survivals does not depend on it.

To our knowledge, our study is the largest series about the relationship between endobronchial lesions and lymph node metastasis in Turkey. However, it has several limitations including being a retrospective and single-center study, thus providing a limited contribution to other staging studies.

In conclusion, N_1 positivity was significantly more frequent in non-small cell lung cancer cases with endobronchial lesions, which raises the suspicion that metastasis may develop via the peribronchial lymphatics. Also, since we showed that the survival of patients with endobronchial lesions was much better than those with peripheral tumors, the presence of endobronchial component may be shown in good prognostic factors. However, further clinical studies are needed to clarify this issue.

Declaration of conflicting interests

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