

Factors Effecting Long-term Survival in Operated Large Cell Carcinoma of the Lung

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ABSTRACT

The aim of this study was to evaluate of the results of the treatment of patients who underwent surgery due to large cell lung carcinoma and to analyze the variables affecting the survival outcomes. Pulmonary resections were performed on 1221 patients with pathological stages I, II, III non-small cell lung cancer between January 2003 and January 2013. A total of 85 patients (7%) who were histologically diagnosed with large cell lung carcinoma and 10 patients were excluded from the study because of operative mortality, incomplete resection, and follow-up. The records of 75 patients undergoing complete resection were evaluated in terms of demographics, survival rates, and variables affecting the survival. Seventy-one (94.7%) male and four (5.3%) female patients with a mean age of 58.1±9.8 years (range: 38 to 76 years) were included in the study. Neoadjuvant treatment was administered to four (5.3%) patients. Lobectomy was performed on 53 (70.7%) patients and 28 (37.3%) had neuroendocrine differentiation (NED) in their tumors. Median and five-year survival rates were 80.8 months and 51.1%, respectively in a mean follow-up period of 34.9±27.7 months (range: 2.4 to 91.6 months). Five-year survival rates in the groups with and without neuroendocrine differentiation were 37.8% and 57.9%, respectively, with no statistically significant difference between the groups (p=0.53). The absence of lymph node metastasis and adjuvant treatment had positive effects on survival in patients with large cell lung carcinoma who underwent resection. Although not statistically significant, neuroendocrine differentiation led to a lower survival rates.

Keywords: Large cell lung carcinoma, Neuroendocrine differentiation, Surgery, Survival

ÖZET

Opere Edilmiş Büyük Hücreli Akciğer Karsinomunda Uzun Dönem Sağkalımı Etkileyen Faktörler

Bu çalışmada büyük hücreli akciğer kanseri nedeniyle cerrahi tedavi uygulanan hastaların tedavi sonuçlarının analiz edilmesi ve sağkalım sonuçlarına etkili değişkenlerin araştırılması amaçlanmıştır. Ocak 2003-2013 arasında 1221 hastaya evre I, II ve III küçük hücreli dışı akciğer kanseri nedeni ile lobektomi veya pnömonektomi uygulandı. Bu hastalardan 85'i (%7) histolojik olarak büyük hücreli karsinom tanısı aldı ve 10 hasta operatif mortalite, inkomplet rezeksiyon ve inkomplet izlem nedeniyle çalışma dışı bırakıldı. Komplet rezeksiyon uygulanmış 75 hastanın tıbbi kayıtları, demografik özellikleri ve sağkalım oranları ile sağkalıma etkili değişkenler açısından değerlendirildi. Çalışmaya yaş ortalaması 58.1±9.8 (38 ile 76 arası) olan 71 (%94.7) erkek ve 4 (%5.3) kadın hasta alındı. Dört hasta (%5.3) neoadjuvan tedavi aldı. Lobektomi uygulanan 53 (%70.7) hasta bulunuyordu ve 28 (%37.3) hastada nöroendokrin diferansiasyon (NED) mevcuttu. Ortalama 34,9±27,7 aylık (2,4 ile 91,6 ay arası) takipte median ve 5 yıllık sağkalım oranı 80.8 ay ve %51.1 idi. Nöroendokrin diferansiasyon saptanan ve saptanmayanlarda 5 yıllık sağkalım oranları sırası ile %37.8 ve %57.9 idi ve arada istatistiksel olarak anlamlı bir fark saptanmadı (p=0.53). Bu çalışmada rezeke edilen büyük hücreli akciğer karsinomlu hastalarda, lenf bezi metastazının olmaması ve adjuvan tedavi uygulananın sağkalıma etkisinin daha iyi olduğu saptandı. İstatistiksel olarak anlamlı olmasa da nöroendokrin diferansiasyon, daha kötü bir sağkalım oranı göstermiştir. Ancak lokal yayılım izlenmeyen ve adjuvan tedavi uygulanan hastalarda sağkalım sonuçlarının daha iyi olması beklenebilir.

Anahtar Kelimeler: Büyük hücreli akciğer karsinomu, Nöroendokrin diferansiasyon, Cerrahi, Sağkalım

INTRODUCTION

The term large cell lung carcinoma (LCC) includes a group of tumors that are not included in the other classifications of lung carcinoma, due to histopathological specifications. Its frequency among all the lung cancers is reported to be 9%.¹ Microscopically, they are tumors including organoid and trabecular cells and have high mitotic activity and diffuse necrotic areas.² In addition to the histopathological differences, neuroendocrine differentiation (NED) can also be observed in these tumors in which the response to treatment and prognosis are also unique. The presence of NED in large cell carcinomas places them in the group of neuroendocrine tumors of the lungs.³ The prognosis in those patients with large cell neuroendocrine carcinoma (LCNEC) of the lungs is considered to be between small cell lung cancer (SCLC) and atypical carcinoid tumors of this group. LCCs have been treated similarly to NSCLC; however, a controversial issue in recent years is whether the prognosis of these tumors are close to the prognosis of small cell lung cancer in case NED is detected in these tumors. Therefore, it is important for this group of patients to benefit from complete lung resections. The current study analyzed patients who underwent surgical resection due to large cell lung cancer, the frequency of neuroendocrine differentiation and its effect on survival, together with other factors.

PATIENTS AND METHODS

A total of 1221 patients who underwent surgery for non-small cell lung cancer (NSCLC) between 2003 and 2013 were retrospectively reviewed. There were 85 patients (7%) with a histopathological diagnosis of large cell lung cancer (LCC) among these patients. Ten patients were excluded from the study due to operative mortality, incomplete resection, and incomplete follow-up. Presence of neuroendocrine phenotype was confirmed with immunohistochemical staining methods in 28 out of 75 patients (37.3%) and these patients were identified as the NED (+) group. The rest of the patients (n= 47; 62.7%) represented the NED (-) group. A diagnosis of large cell neuroendocrine carcinoma (LCNEC) was made when all WHO classification criteria were present in the histopathological examination.

Chest X-ray, computed tomography (CT), and fiber optic bronchoscopy were used for loco-regional assessment of lung cancer. Clinical N2 status was defined by the presence of a lymph node measuring greater than 1 cm in the short axis diameter on CT. PET/CT scan was used for distant organ metastasis after 2006 and invasive mediastinal staging (cervical mediastinoscopy) was performed to detect possible mediastinal lymph node metastases according to the scanning results. The pulmonary function was routinely evaluated using spirometry and arterial blood gas analysis. Carbon monoxide diffusion capacity and quantitative ventilation perfusion lung scan was done on patients with an impaired pulmonary reserve (estimated post-resection FEV1 of less than 60%). All patients underwent complete resection (lobectomy, bilobectomy, sleeve lobectomy, or pneumonectomy). Segmentectomy was not performed.

The patients were evaluated in two groups in terms of demographics, preoperative and postoperative management, and survival rates and variables affecting the following parameters: NED (+) group with observation of neuroendocrine differentiation and the NED (-) group without observation of neuroendocrine differentiation.

Statistics

The statistical analysis was conducted using the SPSS package (SPSS, Chicago, IL). Survival was analyzed using the Kaplan-Meier method and the curves were compared using a log-rank test. Multivariate analysis was performed using the Cox proportional hazard model. Frequency comparisons were carried out by Pearson's chi-square test and Fisher's exact test. Results were considered significant at $p < 0.05$.

RESULTS

Seventy-five patients included 71 males and 4 females, indicating a significantly greater number of male patients. The average age at presentation was 58.1 ± 9.8 years (range: 38 to 76 years). Seventy-one patients (94.7%) were current or former smokers. Demographic features of the patients [age, gender, the application of neoadjuvant or adjuvant therapy,

Table 1. Characteristics of the two groups of patients (depending on NED)

Variables	Total		NED (-) group		NED (+) group		p-value
	n	%	n	%	n	%	
Total	75	100	47	62.7	28	37.3	-
Sex							
Male	71	94.7	46	97.9	25	89.3	0.14
Female	4	5.3	1	2.1	3	10.7	
Age							
≤ 60	39	52	24	51.1	15	53.6	1
> 60	36	48	23	48.9	13	46.4	
Neoadjuvant therapy							
Absent	71	94.7	45	95.7	26	92.9	0.63
Present	4	5.3	2	4.3	2	7.1	
Operation type							
Lobectomy	53	70.7	33	70.2	20	71.4	0.35
Sleeve lobectomy	10	13.3	8	17	2	7.1	
Pneumonectomy	12	16.0	6	12.8	6	21.4	
Tumor type							
≤ 3 cm	19	25.3	9	19.1	10	35.8	0.26
3-5 cm	26	34.7	17	36.2	9	32.1	
> 5 cm	30	40	21	44.7	9	32.1	
p-T							
I	13	17.3	7	14.9	6	21.4	0.74
II	41	54.7	27	57.4	14	50	
III	21	28	13	27.7	8	28.6	
p-N							
0	54	72	34	72.3	20	71.4	0.56
1	10	13.1	5	10.6	5	17.9	
2	11	14.7	8	17	3	10.7	
p-stage							
1	27	36	17	36.2	10	35.7	0.95
2	28	37.3	18	38.3	10	35.7	
3	20	26.7	12	25.5	8	28.6	
Smoking							
Absent	4	5.3	4	8.5	0	0	0.28
Present	71	94.7	43	91.5	28	100	
Adjuvant therapy							
Absent	52	69.3	33	70.2	19	67.9	1
Present	23	30.7	14	29.8	9	32.1	

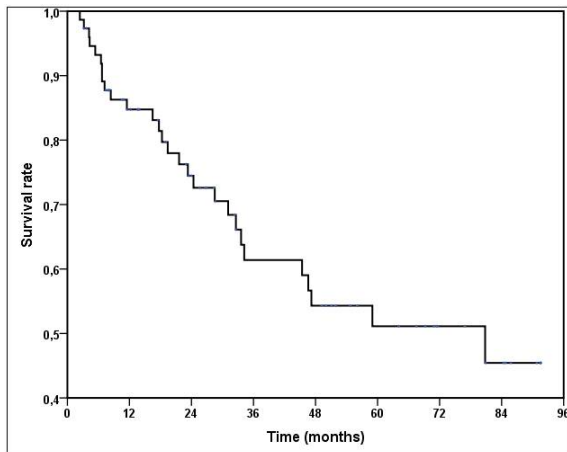


Figure 1. Kaplan-Meier five-year survival estimates for all 75 patients

operation type [lobectomy, sleeve lobectomy, or pneumonectomy], tumor diameter, pathological stage, and smoking] are given in Table 1. An en bloc resection of the chest wall was additionally performed in four lobectomy cases. PET/CT was obtained in 34 (47%) cases and 10 (13%) cases underwent mediastinoscopy for lymph node staging according to the results.

Endobronchial lesions were seen in 16 cases (21%) in the fiber optic bronchoscopy (FOB). The endobronchial localization was as follows; in three (4%) cases the tumor was in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina, in three (4%) cases the tumor involved the main bronchus, but was 2 cm or more

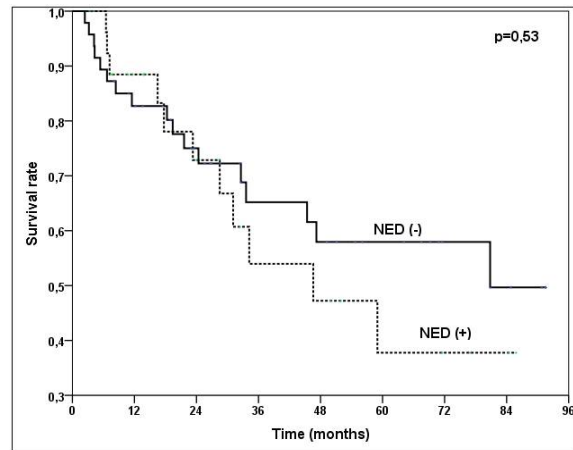


Figure 2. Five-year survival curves in patients with NED (neuroendocrine differentiation) (dashed line) and without NED (straight line) ($p=0.53$).

distal to the carina, in four (5%) cases the tumor was in the proximal lobar bronchus, in six (8%) cases the tumor was in the segmental bronchus, and in 59 (79%) cases the tumor was peripherally located.

Platinum-based neoadjuvant chemotherapy was administered to only four (5.3%) cases due to mediastinal lymph node metastasis, and postoperative chemotherapy (CT) and/or radiotherapy (RT) was administered to 23 (30.7%) cases (CT in 17 cases, RT in five cases, and CT+RT in one case).

Overall survival curve for the 75 accurately staged patients with complete resection was 51.1% at five years, as shown in Figure 1. In addition, survival curves were created for neuroendocrine differenti-

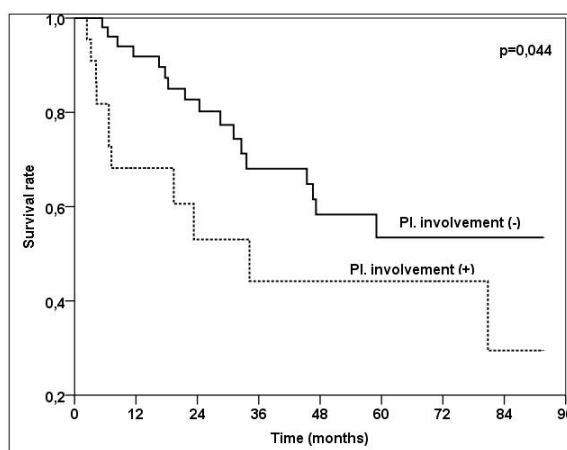


Figure 3. Five-year survival curves in patients with (dashed line) and without (straight line) pleural metastasis ($p=0.044$)

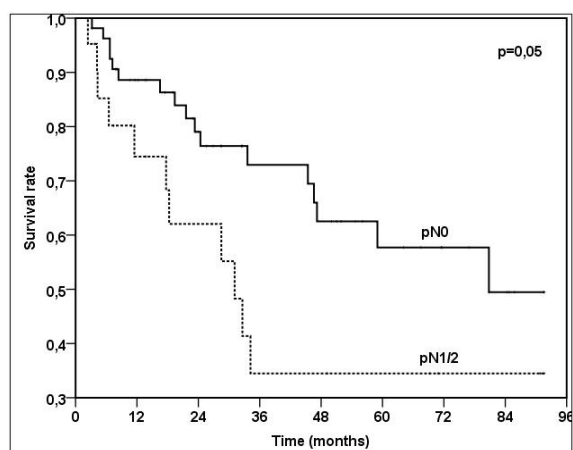


Figure 4. Five-year survival curves in patients with (dashed line) and without (straight line) lymph node involvement ($p=0.05$)

Table 2. Univariate analyses of prognostic factors in surgically resected large cell carcinoma of the lung

Variables	5-year survival. %	Mean survival (months±SD)	Confidence interval	p-value
Total	51.1	58.38±4.69	49.18 - 67.57	-
Disease-free	50.8	55.8±5.03	45.94 - 65.65	-
Sex				
Male	55.9	60±4.88	50.45 - 69.55	0.19
Female	0	41.3±12.04	17.69 - 64.91	
Age				
≤ 60	47.3	57.09±6.84	43.69 - 70.49	0.95
> 60	54.7	59±6.5	46.27 - 71.73	
Neoadjuvant therapy				
Absent	51.5	58.73±4.73	49.46 - 68.00	0.54
Present	75	12.05±1.60	8.91 - 15.19	
Operation type				
Lobectomy	56.3	63.7±5.5	52.8 - 74.5	0.12
Sleeve lobectomy	53.3	52±13.3	26.8 - 78.7	
Pneumonectomy	23.6	35.7±7.5	21.1 - 50.3	
Tumor size				
≤ 3 cm	44	53.04±7.77	37.81 - 68.28	0.74
3-5 cm	62.6	65.22±8.26	49.03 - 81.41	
> 5 cm	46.8	54.64±7.04	40.84 - 68.44	
p-Tumor				
1	34.7	51.39±9.06	33.63 - 69.14	0.69
2	55.6	62.33±6.34	49.90 - 74.76	
3	50.8	52.76±8.91	35.30 - 70.22	
p-Node				
0	57.7	64.1±5.3	53.80 - 74.42	0.05
1/2	34.5	52.3±11.6	29.6 - 75.0	
p-stage				
1	52.5	57.81±6.43	45.20 - 70.41	0.29
2	55	60.97±7.06	47.15 - 74.80	
3	40.3	46.92±10.16	27.01 - 66.83	
NED				
Absent	57.9	61.08±5.79	49.74 - 72.42	0.53
Present	37.8	50.83±7.15	36.81 - 64.84	
Pleural metastasis				
Absent	53.5	63.14±5.31	52.73 - 73.55	0.044
Present	44.2	46.7±9.3	28.4 - 65.0	
Present	52.8	58.93±9.32	40.67 - 77.19	

SD: Standard deviation. p-stage: pathological stage. NED: Neuroendocrin differentiation.

Table 3. Multivariate analyses of prognostic factors in surgically resected large cell carcinoma of the lung

Variable	p-value
P-node metastasis, N0 vs. N1 and N2	0.027
Operation type, lobectomy, sleeve lobectomy vs. pneumonectomy	0.52
Neoadjuvant chemotherapy, present vs. absent	0.56
Adjuvant chemotherapy, present vs. absent	0.029
Pleural metastasis, present vs. absent	0.14
P-stage, P-stage I vs. P-stage II and P-stage III	0.99
NED, present vs. absent	0.53

p-stage: pathological stage. NED: Neuroendocrine differentiation.

ation (Figure 2), pleural metastasis (Figure 3), and lymph node metastasis (Figures 4).

The influence of age, gender, neoadjuvant therapy, operation type, tumor size, pathologic T, pathologic N, pathologic stage, and neuroendocrine differentiation were evaluated by univariate analysis (Table 2). The multivariate analysis in our series identified predictors of survival (Table 3).

Follow-up

Four patients (5%) dropped out of the follow-up during the study period. The follow-up for this group ranged from 2.4 months to 105.6 months. The median follow-up time was 34.9±27.7 months. Twelve patients (16%) died of causes other than neoplastic disease, and 17 patients (23%) died of metastatic spread. Four (5%) loco-regional recurrences were noted.

DISCUSSION

Pleural metastasis (p= 0.05) and lymph node metastasis (p= 0.044) were associated with poorer overall survival for large cell carcinoma (LCC) after complete resection in univariate analyses, but no other variables had an effect on survival in these patients. In addition, the multivariate analysis also showed that lymph node metastasis had a negative effect (p= 0.027) where adjuvant therapy (p=

0.029) positively affected survival of LCC patients. None of other variables were statistically significant. The median and five-year survival was much higher in the NED (-) group compared to the NED (+) group (57.9% versus 37.8% and 80.8 months versus 46.6 months, respectively); however, it is noteworthy that we found no significant difference in survival between patients with NED (+) group and the NED (-) group.

Following the classification of the neuroendocrine tumors of the lungs in the 1970s as typical carcinoid tumors, atypical carcinoid tumors and small cell carcinomas⁴, Travis et al.⁵ introduced the concept of large cell neuroendocrine carcinoma (LCNEC) as a subgroup of neuroendocrine tumors in 1991. LCNEC was classified in an intermediate position between atypical carcinoid and small cell lung carcinoma according to its clinically aggressive behavior.⁶ Finally, it was defined as a variant of large cell carcinoma in 1999 and later in 2004 by the World Health Organization (WHO).^{3,7} According to these studies, the main criteria for diagnosing LCNEC are: (A) large cell morphology; (B) high mitotic rate of more than 11 or greater/10 high power fields; and (C) the detection of neuroendocrine morphology and immunohistochemical markers. However, it became clear that the clinical and biological features of LCNEC are similar to those of small cell lung carcinoma (SCLC), and the differential diagnosis between LCNEC and SCLC is quite difficult in some cases.^{8,9,10}

Park et al. demonstrated that the preoperative diagnosis for LCC is sometimes difficult because of the small sample obtained in lung biopsies.¹¹ Larger surgical specimens often yield more information, and the diagnosis often changes to adenocarcinoma or squamous cell carcinoma. It is difficult to distinguish a poorly differentiated squamous cell carcinoma or adenocarcinoma preoperatively because of the indefinite diagnosis criteria. In this study, preoperative fine-needle aspiration biopsy was inconclusive for tumor type in 16 out of 75 patients (21%) and a definitive diagnosis was possible only in the perioperative period. Preoperative cisplatin-based chemotherapy was administered in four cases (5.3%) in this study and all of them responded to the treatment. However, the clinical characteristics and optimal treatment of large cell carcinomas (LCC) have not yet been clearly identified. Large series, especially on large cell carcinomas demonstrating neuroendocrine behavior, are rare.

The absence of large series in the literature is a serious problem in creating a definitive treatment strategy in LCC. A surgical approach to cases with these tumors was recommended to be similar to the cases with non-small cell lung cancers (NSCLC).¹² In addition, according to the Guidelines of the National Comprehensive Cancer Network, the treatment of these tumors was suggested to be similar to non-small cell lung cancers.¹³ Many studies suggest a better prognosis be obtained with complete resection and systematic nodal dissection.^{14,15,16}

The efficacy of cisplatin-based chemotherapy in patients with LCNEC and small cell carcinomas were found to be similar to the reported objective response of 50%.¹⁷ Survival rates were demonstrated to be significantly increased with surgery and adjuvant therapy in an early stage LCNEC series (n= 73) of Iyoda et al.¹⁸ In the present study, on the other hand, adjuvant therapy was applied to the locally advanced cases. Although the group of patients receiving adjuvant therapy in his study (n= 23; 31%) was at a more advanced stage of the disease, the five-year survival in this group was slightly higher compared to the group of early stage patients (n= 52, 69%) who did not receive adjuvant therapy; however, the difference was not statistically significant (52.8% vs. 49.8%; p=0.75).

LCC is generally seen in men with a mean age in the sixth decade of life.¹⁴⁻¹⁸ The mean age was 63.7 years in a series of patients with LCNEC in a study of ten years' of experience reported by Paci et al.¹⁵ Males comprised 94.7% of the cases in the present series (97.9% and 87.3% in the groups with NED (-) and NED (+) cases, respectively). Overall mean age was 58.1 years (range: 38-76 years); and was 58.4 years (range: 38-76 years), and 57.5 (range: 41-73 years) in NED (-) and NED (+) cases, respectively.

A history of cigarette smoking is a specifically emphasized issue in the studies concerning cases with LCNEC.^{12,15,19,20} It is such a rare event that one case with LCNEC without a history of cigarette smoking was reported in a case report in the literature.²² In those cases, a mixed tumor is generally present.^{19,21,22} Takei et al. reported that 98% of their large LCNEC series of 87 cases were cigarette smokers.¹⁹ The history of cigarette smoking was positive in most of our cases (94.7%); however, no mixed tumors were detected.

Symptoms of LCC are nonspecific, such as coughing and hemoptysis, which are also seen in other lung tumors. Findings such as flushing, wheezing, and diarrhea can be seen in cases with NED¹³; however, none of these symptoms were present in the NED (+) group of patients in this study.

An extremely rare incidence of endobronchial localization has been reported in some series.^{15,22} However, of 63 patients, no endoluminal lesions were seen in 31 cases (49.2%) in the fiber optic bronchoscopy (FOB) (10). Park et al. detected a visible mass in the FOB in 38.4% of the patients who were diagnosed with LCC (10/26).¹¹ We detected endobronchial lesions using fiber optic bronchoscopy in 21% (16/75) of the cases. Most of the 16 cases (21%) with endobronchial lesions were in the NED (+) patient group (n= 10; 13%). In addition, since LCNECs generally have a peripheral localization, findings of post-obstruction are rare.^{13,15,20} Endobronchial localization was detected in 16 (21%) patients with post-obstruction atelectasis in only six (8%) patients in this study. Four of these patients (5%) were in the NED (+) group. Tumoral calcification was absent in all patients in preoperative CT.

Mean five-year survival was reported to be 57% in a large series of LCNEC by Takei et al., while the figure was 51% in our series and 38% in patients with detected NED.¹⁹ Cases with LCNEC deserve much greater attention in the literature among the LCCs; however, the effects of NED positivity on survival with evaluation of all cases, as is the case in the current study, have not been extensively reported. A statistically significant effect of NED on survival was not found in the current study; however, some studies have reported its negative effect on survival.¹⁸⁻²³

Lymph node involvement in the mediastinum was identified in 28% of the cases in a series by Takei et al.¹⁹ In the study of Iyoda et al., five-year survival was 51.7% for LCNEC, which was statistically lower than cases with LCC ($p=0.0321$).¹⁸ On the other hand, the high mitotic activity in those cases of LCNEC was emphasized in that study. The five-year overall survival for resected LCNEC in different studies was 13-51%.^{10,15,19,23,24} Pathological N1 (five patients each in the NED (-) and NED (+) groups, respectively) and N2 (eight and three patients in the NED (-) and NED (+) groups, respectively) were detected in 10 and 11 patients, respectively. Overall survival in patients with pN1 and pN2 was 41.1% (60% and 0% in the NED (-) and NED (+) groups, respectively; $p=0.42$) and 28.9% (40% and 0% in the NED (-) and NED (+) groups, respectively; $p=0.40$), respectively. Overall survival was 57.7% in cases with pN0 (60.2% and 53.0% in the NED (-) and NED (+) groups, respectively; $p=0.96$).

Rates of pneumonectomy were reported to be between 2 and 23% in the studies performed.^{10,15,19,23,25} Lobectomy, sleeve lobectomy and pneumonectomy were performed in 53 (70.7%), (13.3%) and 16 (12%) patients, respectively. The most common indication for pneumonectomy was fissure invasion (16/22 patients, 72.7%). There were no statistically significant differences in survival between the patients who underwent lobectomy and pneumonectomy ($p=0.55$).

The present study had several limitations. It was retrospective in design and involved a relatively small number of patients. Additionally, some of the patients did not undergo PET-CT scan. A prospec-

tive study with a large number of patients and with well-defined inclusion and exclusion criteria could overcome these limitations.

In conclusion, neuroendocrine differentiation seemed to result in a decreased survival rate, although it was not statistically significant. The absence of lymph node metastasis and the application of adjuvant treatment were found to positively affect survival in patients with resected large cell carcinoma. Therefore, it is suggested that adjuvant treatment should be applied to these patients.

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