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The Effects of Tumor Localization on Small Cell Lung Cancer and its Association With Prognosis

Tümör Lokalizasyonunun Küçük Hücre Akciğer Kanseri Üzerine Etkileri ve Prognoz İle İlişkisi

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ABSTRACT

Introduction: Lung cancer is classified as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), both as pathological subtypes. SCLC is associated with a significantly short life expectancy, and it constitutes 10-15% of all lung cancers. Previous studies showed that lung cancer is mostly dominated by the upper lobe and is more common in the right lung than in the left. The principle aim of this study is to analyze the localization of the tumor in the right and left lung in aggressive and malignant SCLC patients by comparing it with determinants such as anatomical features, demographic features, laboratory features, including the association with peripheral-central localizations, especially overall survival.

Methods: There were four hundred forty-six lung cancer patients diagnosed in a chest diseases clinic in a tertiary training and research hospital between 2014-03-31 and 2020-03-31. Of these, twenty percent (n=90) were diagnosed as SCLC. Among ninety patients, six were excluded from the study due to incomplete medical SCLC records, and finally, eighty-four patients with SCLC were included in the study.

Results: We classified eighty-four patients into two groups as right and left lung localized SCLC and analyzed all the data. We found that the left lung tumor group had the more extensive-stage disease and had significantly high CRP levels (p=0.027, p=0.045, respectively). When we analyzed the data, such as demographic characteristics, diagnostic methods, overall survival, treatment characteristics, stage characteristics, anatomical features of the right and left tumor groups, we found that there were no significant differences. We used univariate and then multivariate analysis for survival. We found that being sixty-five years old and over (p=0.014), high CRP levels (p=0.016), having centrally localized tumors (p=0.01), having poor performance status (p<0.0001), and having no treatment for primary cancer (p=0.001) were associated with worse survival.

Conclusion: Primary treatment of SCLC patients should start promptly. We found that the central location of the tumor as anatomical localization may be associated with worse survival and that the left lung tumor group had the more extensive-stage disease, with significantly high CRP levels. Being sixty-five years old and over, high CRP levels, having poor performance status and having no treatment for primary cancer, were all significantly associated with worse survival.

Keywords: Small-cell lung cancer (SCLC), survival, tumor localization, prognosis

ÖZ

Amaç: Akciğer kanseri, patolojik alt tipler olarak küçük hücreli dışı akciğer kanseri (KHDAK) ve küçük hücreli akciğer kanseri (KHAK) olarak sınıflandırılır. KHAK, önemli ölçüde kısa bir yaşam beklentisi ile ilişkilidir ve tüm akciğer kanserlerinin %10-15'ini oluşturur. Önceki çalışmalar, akciğer kanserinin çoğunlukla üst lobun baskın olduğunu ve sağ akciğerde sola göre daha yaygın olduğunu gösterdi. Bu çalışmanın temel amacı, agresif ve malign KHAK hastalarında tümörün sağ ve sol akciğerdeki lokalizasyonunu anatomik özellikler, demografik özellikler, laboratuvar özellikleri gibi belirleyicilerle karşılaştırarak periferik-merkezi yerleşimlerle ilişkisini de içerecek şekilde analiz etmek ve özellikle de sağkalımı değerlendirmektir.

Metot: Bir üçüncü basamak eğitim ve araştırma hastanesinde göğüs hastalıkları kliniğinde 31.03.2014-31.03.2020 tarihleri arasında tanı almış 446 akciğer kanseri hastası tespit edildi. Bunların %20'si (n=90) KHAK tanısı aldı. Doksan hastadan altı tanesi eksik tıbbi kayıtları nedeniyle çalışma dışı bırakıldı ve son olarak KHAK'lı 84 hasta çalışmaya dahil edildi.

Bulgular: 84 hastamızı sağ ve sol akciğerde lokalize KHAK olarak iki ana gruba ayırdık ve tüm verileri analiz ettik. Sol akciğer tümörü grubunun daha yaygın evreli hastalığa sahip olduğunu ve anlamlı derecede yüksek CRP düzeylerine sahip olduğunu bulduk (sırasıyla p=0.027, p=0.045). Sağ ve sol tümör gruplarının demografik özellikleri, tanı yöntemleri, genel sağkalım, tedavi özellikleri, evre özellikleri, anatomik özellikleri gibi verileri analiz ettiğimizde istatistiksel olarak anlamlı bir fark olmadığını gördük. Tüm verilerimizin sağkalım açısından önce tek değişkenli analiz, ardından çok değişkenli analiz ile analiz edilmesi sonucunda; 65 yaş ve üzeri (p=0.014), CRP yüksekliği (p=0.016), santral yerleşimli tümör varlığı (p=0.01), performans düşüklüğü (p<0.0001) ve primer tedaviyi almayan kanser durumu (p=0.001) daha kötü sağkalım ile ilişkilendirildi.

Sonuç: KHAK hastalarının ilk tedavisi hemen başlanmalıdır. Anatomik lokalizasyon olarak tümörün merkezi yerleşiminin daha kötü sağkalım ile ilişkili olabileceğini bulduk. Ayrıca sol akciğer tümörü grubunun daha yaygın evreli hastalığa sahip olduğunu ve CRP düzeylerinin anlamlı derecede yüksek olduğunu bulduk. Altmışbeş yaş ve üstü olmak, yüksek CRP düzeyleri, düşük performans durumuna sahip olmak ve primer kanser tedavisi görmemek, daha kötü sağkalım ile anlamlı olarak ilişkiliydi.

Anahtar sözcükler: Küçük hücreli akciğer kanseri, sağkalım, tümör lokalizasyonu, prognoz

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INTRODUCTION

Lung cancer is classified as small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), both as pathological subtypes [1]. SCLC is associated with a significantly short life expectancy and constitutes 10 to 15% of all lung cancers [2]. It has a short tumor doubling time and is highly invasive [1]. SCLC is more sensitive to chemotherapy and radiation but its prognosis is the poorest: the overall survival rate for five years is only 5 to 15% [3]. While NSCLC types are examined in four stages with the TNM Classification of Malignant Tumours (TNM) [4], SCLC is typically evaluated into two main categories: limited-stage and extensive-stage. In parallel with the developments in SCLC treatment since the 1970s, there have been improvements in the overall survival rate [5].

It has been inferred from previous studies that lung cancer is mostly dominated by the upper lobe and is more common in the right lung than the left [6,7]. Atypical malignancy localizations, such as the trachea, have also been reported in the literature [8]. No statistical association was found between the anatomical localization of the tumor on the right lung or the left lung and the survival of the patient in SCLC, in the previously analyzed limited data [6,9]. There exists varying reports regarding the association between localization of the tumor (central or peripheral tumor) and survival, in SCLC [3,10,11].

The principal aim of this study was to analyze the localization of the tumor in the right and left lung in aggressive and malignant SCLC cases, by comparing it with variables such as anatomical features, demographic features, laboratory features, including the association with peripheral-central localizations, and in particular with overall survival. In addition, we aimed to analyze the prognostic factors related to survival.

MATERIAL AND METHOD

Study population

There were four hundred forty-six lung cancer patients diagnosed in a chest diseases clinic in a tertiary training and research hospital, between March 31st, 2014 and March 31st, 2020. Of these patients, 33% (n=148) were diagnosed as squamous cell lung carcinoma, 32% (n=142) were diagnosed as adenocarcinoma, 8% (n=36) were diagnosed as NOS (not otherwise specified), 7% (n=30) were diagnosed as other primary lung cancers and finally, 20% (n=90) were diagnosed as SCLC. Among ninety patients, 6 were excluded from the study as a result of incomplete medical records so that at the final onset of the study, 84 patients with SCLC were included (Figure 1).

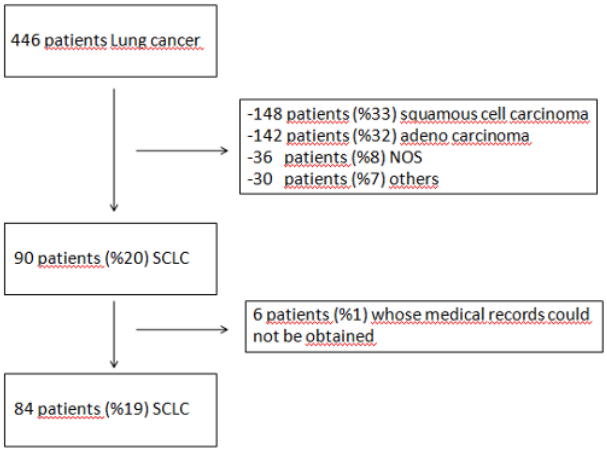

Figure 1. Patients' flowchart

As recommended by the guidelines, follow-ups were performed with Thorax CT and/or PET-CT every 3 months for the first 2 years, every 6 months for 2 to 4 years, and once a year for more than 4 years. The data of the cases in our study is right-stopped data ending on March 31st, 2020 (our last patient date). As of the end of our study, 18 patients were still alive and those were followed for at least one year. When all cases (n=84) were included, our median follow-up was 8.05 months (0.2-70 months).

All patients were over 18 years old, with a pathological diagnosis of SCLC, with complete radiological PET-CT examination and medical records. The treatment schemes of 67 patients who received treatment were reviewed. Cisplatin/Carboplatin and Etoposide treatment followed by curative radiotherapy (n=16) were applied to all limited-stage cases. Cisplatin/Carboplatin and Etoposide treatment were applied to all cases with extensive stage.

Design

The SCLC patients were divided into two main

groups in terms of anatomical localization (Figure 2: right and left lung tumors). For these two groups, demographic characteristics, accompanying diseases, radiological features, treatment features, laboratory parameters, TNM staging features, and limited and extensive stages (the Eighth Edition Lung Cancer Stage Classification), were analyzed. In addition, the presence of peripheral tumors and central tumors in these two groups was also examined. All variables were examined, and statistical significance was checked. Survival analyses were also conducted.

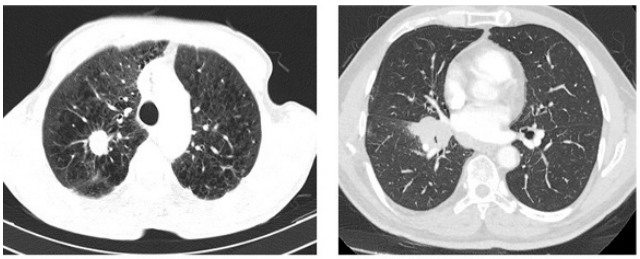

Figure 2. Peripheral and central SCLC

At the time of diagnosis, all cases underwent PET-CT scans and Cranial MRI examinations. Staging, mediastinal lymph node involvement (N1-2-3) and evaluation of metastases were performed with PET-CT. The presence of brain metastases in all cases was evaluated with Cranial MRI. The staging was performed both according to the TNM system and according to limited disease-extensive disease staging.

Definitions

The definitions of the limited and extensive stages were made in line with "The Veterans' Administration Lung Study Group (VALSG) stage classification". This widely accepted classification for SCLC is still used. "VALSG defines limited-stage (LS) as a disease confined to a single hemithorax, including contralateral mediastinal and ipsilateral supraclavicular lymph nodes if all disease can be safely encompassed in a radiation port area. Extensive stage (ES) is defined as a disease that cannot be classified as limited, including malignant pleural or pericardial effusions and hematogenous metastases" [5].

For the definitions of the locations, "central tumor location was defined as within 2 cm of the proximal bronchial tree, heart, great vessels, trachea, or other mediastinal structures" [10]. Tumors outside this definition were defined as peripheral tumors [10] [Figure 2]. Peripheral-central tumor distinctions of all patients were made with Thorax CT.

Statistical analysis

For the distribution of all continuous variable values, the Kolmogorov-Smirnov or Shapiro-Wilk test, coefficient of variation value, Skewness-Kurtosis values, histogram and detrended plot graphs, were examined. Categorical nominal data were indicated as n/%. When the data was ordinal or numeric but not normally distributed, the median was indicated as /min-max and it was indicated as mean/sd for numerical and normally distributed data. In our study group, which we divided into right lung tumor and left lung tumor, categorical data was evaluated with the Chi-square or Fisher test, where appropriate, and numerical data was evaluated with Student's t-test or Mann-Whitney-U test, as appropriate. Survival analyzes were performed with univariate survival analyzes such as the Tiger Meier test, Log Rank test, and multivariate survival analysis in the form of a Cox regression model. The SPSS (Statistical Package for the Social Sciences) statistical software package (version 22) was used and values with a p-value <0.05 were considered statistically significant. The study was approved by the institutional education board of our hospital (date: 2021-06-17 and number: 730)

RESULTS

In this study, among eighty-four SCLC patients, seventy-two were male (85.7%). The mean age at diagnosis was 65.27±9.75. We classified patients into two main groups: 54 patients (64%) with right lung tumor and 30 patients (36%) with left lung tumor (Table 1). A Chi-square test was used for these two groups and it was found that left lung tumors were mostly in the extensive stage of the disease (p=0.027). However, we found that there was no significant difference between the two groups in terms of age, gender, smoking characteristics, performance status, treatments received, overall survival, diagnostic methods and survival status (Table 1).

Fiberoptic bronchoscopy (FOB) was found to be

Table 1. Demographic and basal features

	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Age, median (range)	65.50 (41-87)	65.50 (41-87)	65.50 (48-86)	p=0.46
Sex				p=0.85
Male	72 (85.7%)	46 (85.2%)	26 (86.7%)	
Female	12 (14.3%)	8 (14.8%)	4 (13.3%)	
Smoking (at the time of diagnosis)				p=0.69
Nonsmoker	10 (11.9%)	6 (11.1%)	4 (13.3%)	
Quit	62 (73.8%)	39 (72.2%)	23(76.7%)	
Still smoking	12 (14.3%)	9 (16.7%)	3 (10%)	
Smoking (pack/year) (mean±SD)	33.07±19.34	33.33±19.75	32.6±18.91	p=0.86
ECOG				p=0.94
ECOG 0	7 (8.3%)	5 (9.3%)	2 (6.7%)	
ECOG 1	20 (23.8%)	13 (24.1%)	7 (23.3%)	
ECOG 2	25 (29.8%)	17 (31.5%)	8 (26.7%)	
ECOG 3	16 (19%)	10 (18.5%)	6 (20%)	
ECOG 4	16 (19%)	9 (16.7%)	7 (23.3%)	
Treatment				p=0.49
Only CT	51 (60.7%)	35 (64.8%)	16 (53.3%)	
Curative CRT	16 (19%)	10 (18.5%)	6 (20%)	
Supportive Treatments	17 (20.2%)	9 (16.7%)	8 (26.7%)	
Palliative RT				p=0.93
Received	20 (23.8%)	13 (24.1%)	7 (23.3%)	
Did not receive	64 (76.2%)	41 (75.9%)	23 (76.7%)	
PCI				p=0.25
Received	20 (23.8%)	15 (27.8%)	5 (16.7%)	
Did not receive	64 (76.2%)	39 (72.2%)	25 (83.3%)	
Median overall survival (month)	8.05 (0.2-70)	8.55 (0.20-70)	6.65 (0.3-41)	p=0.76
Survival status				p=0.81
Exitus	66 (78.6%)	42 (77.8%)	24 (80%)	
Survived	18 (21.4%)	12 (22.2%)	6 (20%)	
Diagnostic methods				p=0.15
FOB	59 (70.2%)	42 (78.8%)	17 (56.7%)	
EBUS-TBNA	12 (14.3%)	5 (9.3%)	7 (23.3%)	
TTNB	11 (13.1%)	6 (11.1%)	5 (16.7%)	
Extra thoracic lymph node biopsy	1 (1.2%)	1 (1.9%)	0 (0%)	
Pleural fluid biopsy	1 (1.2%)	0 (0%)	1 (3.3%)	

ECOG: Eastern Cooperative Oncology Group, FOB: Fiber optic bronchoscopy, EBUS-TBNA: Endobronchial ultrasonography- Transbronchial needle aspiration, TTNB: Transthoracic needle biopsy, CT: Chemotherapy, CRT: Chemoradiotherapy, PCI: Prophylactic cranial irradiation

the most common diagnostic method performed on 59 patients (70.2%). Anatomical locations and stage features are shown in Table 2. In the right and left lung tumor groups, there were 79 patients with centrally localized tumors (94%) and 5 patients with peripherally localized tumors (6%). When patients were examined in terms of the TNM classification, limited disease and extensive disease, it was observed that 52.4% (n=44) of patients were in T4, 72.6% (n=61) of patients were in N3, 57.1% (n=48) of patients were in M1c and, 76.2% (n=64) of patients were in extensive-stage. In right and left lung tumor groups, there was no statistical significance in terms of central-peripheral status, tumor size and stage characteristics (Table 2). When the comorbidities and metastasis conditions (Table 3) and laboratory characteristics (Table 4) in the right and left lung tumor groups were examined, it was observed that only the CRP level was statistically significantly higher in the left tumor group (p=0.045).

Table 2. Anatomical localization and stage features

TNM and Tumor localization	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Localization				
Central	79 (94%)	52 (96.3%)	27 (90%)	p=0.243
Peripheral	5 (6%)	2 (3.7%)	3(10%)	
Tumor size (cm)	6.5 (2.2-10.9)	6.4 (2.2-10.9)	6.75 (2.2-10.5)	p=0.98
Tumor				
T1	4 (4.8%)	1 (1.9%)	3 (10%)	
T2	18 (21.4%)	13 (24.1%)	5 (16.7%)	p=0.346
T3	18 (21.4%)	11 (20.4%)	7 (23.3%)	
T4	44 (52.4%)	29 (53.7%)	15 (50%)	
Node				
N1	3 (3.6%)	3 (5.6%)	0 (0%)	p=0.182
N2	20 (23.8%)	15 (27.8%)	5 (16.7%)	
N3	61 (72.6%)	36 (66.7%)	25 (83.3%)	
Metastasis				
M0	26 (31%)	18 (33.3%)	8(26.7%)	
M1a	8 (9.5%)	5 (9.3%)	3 (10%)	p=0.274
M1b	2 (2.4%)	0 (0%)	2 (6.7%)	
M1c	48 (57.1%)	31 (57.4%)	17 (56.7%)	
Stage				
Limited	20 (23.8%)	17 (31.5%)	3 (10%)	p=0.027
Extended	67 (76.2%)	37 (68.5%)	27 (90%)	

Table 3. Comorbid diseases and localizations of metastasis

	Total n=84 (100%) n (%)	Right Lung SCLC n=54 (64%) n (%)	Left Lung SCLC n=30 (36%) n (%)	p-value
Chronic obstructive pulmonary disease	34 (40.5%)	21 (61.8%)	13 (38.2%)	p=0.69
Diabetes Mellitus	9 (10.7%)	4 (44.4%)	5 (55.6%)	p=0.18
Hypertension	34 (40.5%)	22 (64.7%)	12 (35.3%)	p=0.94
Atherosclerotic heart disease	10 (11.9%)	7 (70%)	3 (30%)	p=0.68
Brain metastasis	14 (16.7%)	9 (64.3%)	4 (35.7%)	p=1
Bone metastasis	41 (48.8%)	24 (58.5%)	17 (41.5%)	p=0.28
Liver metastasis	27 (32.1%)	17 (63%)	10 (37%)	p=0.86
Adrenal metastasis	21 (25%)	11 (52.4%)	10 (47.6%)	p=0.18
Lung metastasis	22 (26.7%)	14 (63.6%)	8 (36.4%)	p=0.94
Intraabdominal lymphatic metastasis	12 (14.3%)	10 (83.3%)	2 (16.7%)	p=0.13
Pancreas metastasis	5 (6%)	2 (40%)	3 (60%)	p=0.24
Spleen metastasis	1 (1.2%)	0 (0%)	1 (100%)	p=0.17
Skin metastasis	4 (4.8%)	1 (25%)	3 (75%)	p=0.09

As shown in Table 5, among the study group, 76.2% (n=64) patients had extensive disease and 23.8% (n=20) had limited disease. The extensive disease median overall survival value was 5.7 months (4.446-6.954) and the limited disease median overall survival value was 13.3 months (0.000-28.675) (respectively, p<0.0001, log-rank). We analyzed patients in terms of survival characteristics. Firstly, the data was evaluated with the univariate Kaplan Meier test and the Log Rank test (Figure 3 and 4). As a result, being 65 years or older, having a central tumor, having an extensive stage, having a high-performance status, not receiving treatment for the primary disease, not receiving PCI (prophylactic cranial irradiation), high CRP levels were found to be

Table 4. Laboratory features

Variables	Total n=84 mean (min-max)	Right Lung SCLC n=54 (64%) mean (min-max	Left Lung SCLC n=30 (36%) mean (min-max)	p-value
WBC (x10^3/µL)	9.14 (4.5-18.8)	9.11 (4.76-18.8)	10.02 (4.5-15.5)	p=0.68
Neutrophil (x10^3/µL)	6.15 (1.7-14.64)	5.46 (2.74-14.64)	6.67 (1.7-12.46)	p=0.23
Lymphocyte (x10^3/µL)	1.98 (0.49-5.35)	1.96 (0.49-5.35)	2.08 (0.7-3.59)	p=0.23
NLR	3.07 (0.81-17.4)	2.73 (0.95-11.06)	3.75 (0.81-17.4)	p=0.12
Hemoglobin (g/dL)	13.59±1.93	13.73±1.98	13.35±1.84	p=0.38
Thrombocyte (x10^3/µL)	288 (48.4-1187)	277 (48.4-1187)	300 (145-464)	p=0.72
Creatinine (mg/dL)	0.84 (0.53-1.77)	0.85 (0.59-1.51)	0.83 (0.53-1.77)	p=0.93
Uric Acid (mg/dL)	5.2 (1.5-10.3)	5.2 (2.7-8.8)	5.3 (1.5-10.3)	p=0.70
Albumin (g/L)	38.6 (4.37-48)	39.4 (4.8-48)	37.05 (4.37-43)	p=0.08
AST (IU/L)	22.5 (8-147)	23 (8-147)	21.5 (10-120)	p=0.54
ALT (IU/L)	22 (6-176)	22 (6-176)	21.5 (6-64)	p=0.20
LDH (IU/L)	268 (136-1687)	268 (136-1202)	266 (148-1687)	p=0.44
CRP (mg/L)	20.5 (1-232.1)	12.5 (1-203.5)	24.1 (4.2-232.1)	p=0.045
Sedimentation (mm/hour)	39 (1-120)	39 (1-104)	38 (15-120)	p=0.33

WBC: White blood cell count, NLR: The neutrophil-to-lymphocyte ratio, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase,CRP: C-reactive protein

Table 5. Overall survival analysis of variables with univariate log-rank test and multivariate cox regression model

Variables	n	Median Overall survival (month)	Univariate analysis p-value	Multivariat analysis HR	Multivariat Analysis (95%CI)	Multivariate analysis (p-value)
Age			p=0.016			
<65 years	44	10.7		ref	ref	
≥65 years	40	5.5		1.93	1.140-3.266	p=0.014
Gender			p=0.333			
Male	72	7		-	-	-
Female	12	9.1				
Right or Left Lung			p=0.790			
Right	54	8.6		-	-	-
Left	30	6.5				
Central/peripheral			p=0.010			
Peripheral	5	27.2		ref	ref	p=0.010
Central	79	7		0.068	0.009-0.526	
Disease status			p<0.0001			
Limited	20	13.3		ref	ref	p=0.103
Extensive	64	5.7		1.859	0.882-3.919	
Performance Status			p<0.0001			
ECOG 0-1	27	16.7		ref	ref	p<0.0001
ECOG 2-4	57	5.2		4.660	2.284-9.507	
Treatment status			p<0.0001			
Treated	67	10.2		ref	ref	p=0.001
Non treated	17	1.6		2.928	1.511-5.674	
PCI			p<0.001			
Yes	20	13.3		ref	ref	p=0.883
No	64	5.7		1.058	0.500-2.236	
CRP			p=0.032			
Normal	13	12.1		ref	ref	p=0.016
High (>5 mg/L)	71	6.5		2.631	1.201-5.763	
LDH			p=0.066			
Normal	34	9.1		ref	ref	p=0.100
High (>248 IU/L)	50	6		1.569	0.917-2.686	

ECOG: Eastern Cooperative Oncology Group, PCI: Prophylactic cranial irradiation, LDH: Lactate dehydrogenase, CRP: C-reactive protein

significantly associated with poor prognosis. When these results were analyzed with a multivariate cox regression model afterward, only being 65 years or older (p=0.014), having a central tumor at the time of diagnosis (p=0.01), poor performance status (p<0.0001), not receiving treatment (p=0.001) and high CRP levels (p=0.016) were observed to be significantly associated with poor prognosis.

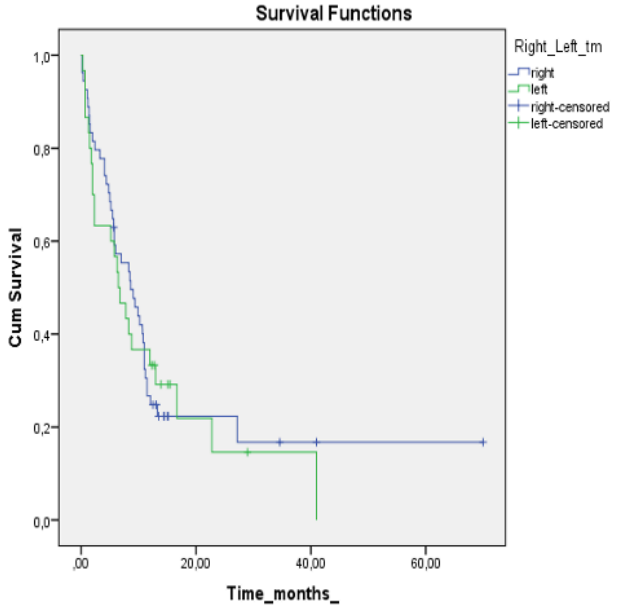

Figure 3. Survival analysis of right and left lung tumor localization with Kaplan-Meier analyze

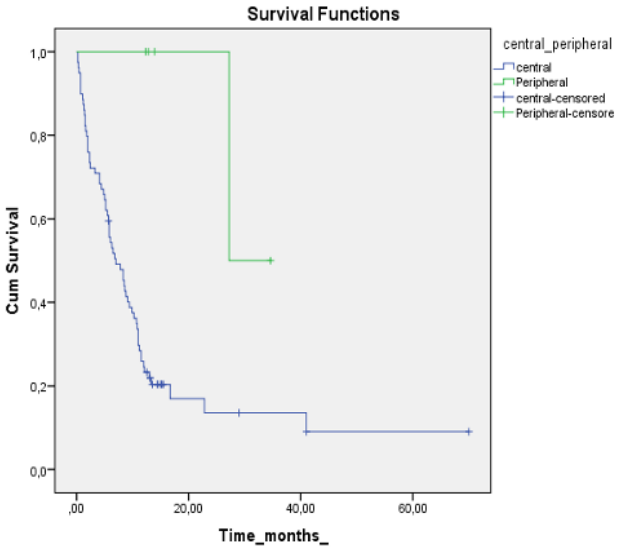

Figure 4. Survival analysis of central and peripheral lung tumor localization with Kaplan-Meier analyze

As a summary, we classified our 84 patients into two main groups as right and left lung localized SCLC and analyzed all the data. We found that the left lung tumor group had the more extensive-stage disease and had significantly high CRP levels (p=0.027, p=0.045, respectively). When we analyzed the data such as demographic characteristics, diagnosis methods, overall survival, treatment characteristics, stage characteristics, anatomical features of the right and left tumor groups, we found that there were no statistically significant differences. As a result of analyzing all our data in terms of survival, with firstly univariate analysis and then with multivariate analysis, we found that being 65 years old and over (p=0.014), high CRP levels (p=0.016), having centrally localized tumors (p=0.01), having poor performance status (p<0.0001), and having no treatment for primary cancer (p=0.001), were associated with worse survival.

DISCUSSION

In previous studies, the median age was 62 years in SCLC patients and 39% were 65 years old and over [12]. In another study, the median age was found as 72 years [11]. In our study, the median age was found to be 65.5 (41-87) consistent with the literature.

Wang et al. evaluated 106 292 SCLC patients and found the median overall survival rate to be seven months [13]. We found the overall survival rate at 8.05 months. Tas et al. found in their study that being older is an independent, poor prognostic factor [14]. When Kanaji et al. evaluated the patient group as the old and young groups, they found that there was no statistical significance in terms of overall survival [11]. In our study, while there was no association between age and right and left lung tumor groups, age was found to be an independent risk factor for survival in the univariate and multivariate analyzes performed for the 65 years old and older group (HR=1.930, p=0.014, Cox model).

The SCLC is more common in males [6,11,15] and this was the case in our study as well. There are studies in which being male was associated with poor survival [9,16] or there was no association between survival and gender [3]. We found no associations between gender and survival.

In the study by Wang et al., primary lesions in the right lung were observed in 126 patients (61.46%), while 79 (38.54%) had primary lesions in the left lung [17]. In another study, Sahmoun et al. also found that the tumors located on the right

lung were common (63%) in the SCLC group [15]. Mennecier et al. found that 53% of patients with SCLC had it on the right-side [18]. In our study, the rate of right-sided tumors (64%) was found to be similar to this previously reported data.

In earlier studies of SCLC, it was found that the right or left localization of the tumor was not associated with survival [6,9]. In our study, we also found no association between right or left localization and survival.

There are studies about the effect of having a peripheral tumor on the prognosis in patients with SCLC. The patients were classified into central and peripheral tumor groups but the results have been inconsistent. In one study, there was no significant prognostic association observed [10] yet in another, peripheral tumors were associated with a poor prognosis [3]. Kanaji et al. for their part found that peripheral tumors were associated with a good prognosis [11]. In our study, the tumors which were centrally located were found to be an independent poor prognostic factor, with the multivariate cox model performed (p=0.01).

Performance status at the time of diagnosis in SCLC patients was usually found poor. Kanaji et al. found that 25% of the patients were Eastern Cooperative Oncology Group (ECOG) class 2 and above, at the time of diagnosis [11]. Le et al. found that 41% of the patients were ECOG class 2 and above at the time of diagnosis [12]. In our study, 67% of the patients were ECOG class 2 and above. Poor performance status was associated with poor survival in SCLC patients in these and other studies [11,12,16]. In our study, poor performance status was found to be an independent risk factor, as a result of the multivariate analysis made with the Cox regression model (HR=4.66, p<0.0001).

In their analysis, Kanaji et al. found that the most commonly used diagnostic procedure was fiberoptic bronchoscopy (68%) [11]. In our study, fiberoptic bronchoscopy was indeed the most commonly used diagnostic method similar to the previous data (70.2%).

The treatment modalities of SCLC were examined in previous studies and approximately 80% of the patients had chemotherapy (CT), or radiotherapy (RT) or chemoradiotherapy (CRT), or Surgery. Approximately 20% of the patients had only the best supportive treatment [6,11]. Median overall survival (OS) with current treatments in SCLC is approximately 20 months for limited-stage (LS) SCLC patients, while it is 8-12 months for extensive-stage (ES) SCLS patients [19].

In our patients, the rates were similar in terms of treatment, 80.7% of them received primary cancer treatment for SCLC, while 19.3% did not. We found the median overall survival to be 13.3 months for our LS-SCLC patients and 5.7 months for our ES-SCLC patients. In this study, consistent with the literature data, primary cancer treatment was found to be associated with better survival (multivariate cox model, p=0.001).

The rate of brain metastasis is found at least 7% at the time of diagnosis [6] but it may increase to approximately 60% in the course of the disease [5]. PCI treatment can reduce the rate of brain metastases by 25% in the course of the disease and increase survival in LS-SCLC patients [20]. PCI treatment can be planned for LS-SCLC and ES-SCLC patients following systemic treatment [5]. In our study, the brain metastasis rate was 16.7% at the time of diagnosis and the number of patients who received PCI was 23.8%. We found that receiving PCI treatment was not statistically significant in terms of overall survival, with the multivariate cox model used.

There is currently no serum biomarker available for the diagnosis of primary SCLC [16]. However, some serum biomarkers are known prognostic factors in SCLC. The high LDH levels were associated with poor prognosis in previous studies [17,21]. Also, high CRP levels at the time of diagnosis were associated with poor overall survival in SCLC [22]. In our study, we analyzed the C reactive protein (CRP) and Lactate dehydrogenase (LDH) levels. High CRP levels were found to be a significantly poor prognostic factor (p=0.024, in the multivariate Cox model). LDH levels were found high in patients who had a worse prognosis, but it was not statistically significant (p=0.082, in the multivariate Cox model).

In our study, we found that there was no significant difference between CRP values and having a central/peripheral tumor and receiving primary malignancy treatment (p>0.05).

Limitations: This study was performed on data from a single-center and this is the main limitation. This study design was cross-sectional, retrospective and comprised patients diagnosed in the last six years and their number was comparatively low, which is our second limitation. The retrospective design was our third limitation.

CONCLUSION

Primary treatment for SCLC patients should start promptly. We found that the central location of the tumor may be associated with worse survival and that the left lung tumor group had the more extensive-stage disease, with significantly high CRP levels. Being 65 years old and over, high CRP levels, having poor performance status and having no treatment for primary cancer, were all significantly associated with worse survival.

CRP elevation was found to be significant among the poor prognostic factors in the univariate (Kaplan-Meier test) analysis and then in the multivariate analysis of our data (cox regression analysis) (p=0.016). Likewise, the presence of a central tumor, poor performance status of the patient and not receiving treatment, were found to be additional poor prognostic factors (p=0.010, p<0.0001, and p=0.001, respectively). These results were found to be compatible with the literature. They also reveal that there is no bias in the selection of the population of our study and the results of the analyzes are compatible with the literature. In addition, we think that if the patients are found to have these poor prognostic criteria at the time of diagnosis, it may be necessary to start the treatment as soon as possible.

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