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Research Article

Factors Affecting Prognosis in Small Cell Lung Cancer

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Abstract

Objectives: Small-cell lung cancer (SCLC) is the most aggressive type of lung cancer. Despite advances in technology and treatments there is no desirable improvement in survival. The present study evaluated the factors affecting survival in patients with SCLC.

Methods: Patients with SCLC followed up in our clinic between 2019 and 2021 were retrospectively reviewed. Univariate and multivariate analyses were performed to identify the prognostic factors. Kaplan-Meier method was used for survival analysis.

Results: The 60 patients comprised 50 (83.3%) men and 10 (16.7%) women with a median age of 61 (53.3-67) years. 40 (66.7%) patients were in extensive stage, 13 (21.7%) patients had brain metastases at the time of diagnosis, and 41 (68.3%) patients had extracranial metastases. There were 18(45%) patients with high serum carcinoembryonic antigen levels and 33 (63%) patients with high lactate dehydrogenase levels at the time of diagnosis. Primer disease control control was achieved in 30 (63%) patients, while Progression developed in 26 (45.6%) patients. Median overall survival was 13 months and it was revealed that survival was better in patients who received ≥4 cycles of chemotherapy, whole-brain radiotherapy, thoracic radiotherapy and disease control.

Conclusion: The success of systemic and local treatment was found to be the most important factor affecting survival in patients with SCLC.

Keywords: Small cell lung cancer, brain metastases, prognosis, systemic treatment effect

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Lung cancer is the leading cause of cancer-related death in the world. Almost 10-20% of patients have brain metastases at the time of diagnosis.[1] Despite the advancements in diagnosis and treatment, average survival is 15-20 months in the limited stage and decreases to 8-13 months in the extensive stage. Factors including advanced age, male gender, metastatic stage, and poor performance status have adverse effects on survival.[2] In addition, the presence, number, and control status of brain metastases and the presence of liver metastasis have also been shown to adversely affect the survival.[3,4] In the literature, various prognostic scoring systems such as Recursive Partitioning Analysis (RPA), Diagnostic-specific Graded Prognostic Assessment (DS-GPA), Basic Score for Brain Metastases (BSBM), and Brain Metastases Score (BMS-Score) have been used to evaluate the prognosis in patients with brain metastases.[5]

Carcinoembryonic antigen (CEA) is a glycoprotein mostly secreted from the gastrointestinal epithelium.[6] In SCLC, 32.8-42.7% of patients have elevated serum CEA levels. Moreover, some studies reported that high CEA levels were associated with negative survival in SCLC with brain me-

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tastasis, while some others did not demonstrate such a relationship.[7,8] Lactate dehydrogenase (LDH) is an enzyme that catalyzes pyruvate conversion to lactate and vice versa. High LDH level is considered to indicate increased tumor burden and cell turnover and decreased survival in many tumors. In addition, high LDH levels have also been correlated with decreased survival in various tumors with brain metastasis.[9,10]

Since SCLC is highly sensitive to chemotherapy and radiotherapy, some patients can be completely cured after such treatments. However, in some patients, relapse may develop in a short time despite a complete response after treatment.[2] In the present study, we aimed to determine prognostic factors of SCLC patients.

Methods

The study protocol was approved by Bursa City Hospital Ethics Committee (Approval Date: 11.08.2021; No:2021-1419). The Institutional Review Board waived the need for informed consent given the retrospective nature of the research. The study was conducted in accordance with the principles laid out by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice and local regulations including local data protection regulations.

The retrospective study included patients with SCLC who applied to Bursa City Hospital Medical Oncology Outpatient Clinic between 2019 and 2021. Patients aged over 18 years who were diagnosed with pathological SCLC and were followed up for more than three months with anticancer treatment were included in the study. Patients who refused to receive anticancer treatment and those who were operated on for a primary lung tumor, had a second malignancy, and had no measurable disease were excluded from the study.

Patients demographic, clinical, tumor pathological and treatment characteristics were evaluated. Overall survival (OS); Time from diagnosis to death or the last follow-up and progression free survival (PFS); Time between the date of progression and the date of diagnosis were calculated. Disease control was accepted as a positive response to first-line treatment. Plasma CEA, LDH, albumin, and sodium levels at the time of diagnosis were assessed using Cobas e 801 analytical unit. Threshold values were accepted as >5.6 ng/mL (high) for CEA, >225 IU/L (high) for LDH, ≤4.34 g/dL (low) for albumin, and Na<135 mEq/L for hyponatremia.

All cranial radiotherapy sessions were performed in the Radiation Oncology department using Elekta Versa HD, Linac device delivering 30 Gy in 10 fractions. An additional boost dose was administered to metastatic sites in patients with brain metastases. In patients with limited-stage disease, thoracic radiotherapy was applied to the primary tumor concurrently with chemotherapy throughout the treatment period. In extensive-stage patients, concomitant platinum-based chemotherapy was administered as systemic first-line therapy. In some selected patients that showed a response to the treatment, thoracic radiotherapy was applied to the primary tumor following chemotherapy.

Statistical Analysis

Data were analyzed using SPSS 23.0 for Windows (Armonk, NY: IBM Corp.). Categorical variables were expressed as frequencies (n) and percentages (%) and continuous variables were expressed as median and quartiles. Survival analysis was conducted using the Kaplan-Meier method. In multivariate analysis, independent factors predicting survival were analyzed using Cox regression analysis with the backward selection method. A p value of <0.05 was considered significant.

Results

The 60 patients comprised 50 (83.3%) men and 10 (16.7%) women with a median age of 61 (range, 53.3-67) years. Of these, 40 (66.7%) patients were in the extensive stage and 20 (33.3%) patients were in the limited stage. Moreover, 51.7% (31/57) of the patients had comorbidities, the ECOG performance status of 38.8% (19/49) of the patients was 0-1, and progression was observed in 45.6% (26/56) of the patients. During the two-year follow-up, mortality occurred in 23 (38.3%) patients (Table 1). In statistical analysis, no significant relationship was found between age, gender, number of cigarettes, presence of comorbidities, ECOG performance status and tumor stage, progression status, and mortality.

Brain metastasis was detected in a total of 17 (28.3%) patients, including 13 (21.7%) metastases detected at diagnosis and 4 (6.7%) metastases detected after diagnosis. No significant correlation was found between age, gender, primary tumor size, stage and the presence of extracranial metastases and brain metastases. The metastasis was solitary in 38% (5/13) of patients detected with brain metastasis at diagnosis. Of all, 64.7% (11/17) of brain metastases were located supratentorially and 47.1% (8/17) of them were single brain metastases. In statistical analysis, no significant relationship was found between OS and the location, number, and size of brain metastases (p=0.451, p=0.195, and p=0.153, respectively). No significant difference was established between patients with and without brain metastases with regard to survival (p=0.706).

Table 1. Demographic, clinical, and pathological characteristics

Clinicopathological characteristics	
Age (years) [median (range)]	61 (53.3-67)
Gender, n (%)	
Male	50 (83.3)
Female	10 (16.7)
Smoking (packs/year) [median (range)]	40 (11.3-60)
Smokers, n (%)	47 (78.3)
ECOG-PS, n (%)	
1	19 (38.8)
2	18 (36.7)
3	12 (24.5)
Tumor size [median (range)]	6.5 (4.4-8.1)
Stage at first diagnosis, n (%)	
Limited stage	20 (33.3)
Extensive stage	40 (66.7)
Brain metastasis	13 (21.7)
Time between first diagnosis and the first appearance of brain metastasis (days) [median (range)]	16 (0-129.5)
Maximum size of brain metastasis (cm?) [median (range)]	2.5 (1.1-3)
Location of brain metastasis, n (%)	
Supratentorial	11 (64.7)
Infratentorial	6 (35.3)
Number of brain metastases, n (%)	
1	8 (47.1)
2	2 (11.8)
>3	7 (41.2)
Size of brain metastasis	
<2.5 cm	8 (47.1)
≥2.5 cm	9 (52.9)
Presence of extracranial metastasis, n (%)	41 (68.3)
Location of extracranial metastasis, n (%)	
Multiple	19 (46.3)
Bone	11 (26.8)
Surrenal	4 (9.8)
Other	7 (17.0)
Presence of comorbidities, n (%)	
Yes	31 (51.7)
No	26 (43.3)
CEA, n (%)	
≤5.6	22 (55.0)
>5.6	18 (45.0)
LDH, n (%)	
Normal	20 (37.0)
High	33 (63.0)
Albumin, n (%)	
≤4.34	46 (80.7)
>4.34	11 (19.3)
Whole-brain Radiotherapy, n (%)	
Yes	23 (40.1)
No	33 (58.9)
Brain surgery, n (%)	
Yes	3 (5.4)
No	53 (94.6)
Hyponatremia, n (%)	
Yes	15 (27.3)
No	40 (72.7)
Weight loss, n (%)	
Yes	6 (17.6)
No	28 (82.4)
Body weight (kg)	
≤60	17 (37.0)
>60	29 (63.0)
Chemotherapy cycles	
<4	11 (19.3)
≥4	46 (80.7)
Thoracic RT	
Yes	18 (33.3)
No	36 (66.6)
Disease control	
Yes	30 (56.6)
No	24 (43.4)
Progression	
Yes	26 (45.6)
No	31 (54.4)
Death	
Yes	23 (38.3)
No	37 (61.7)

ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase; RT: Radiotherapy.

Average primary lung tumor size in 58 patients was 6.5 (range, 4.4-8.1) cm. Extracranial metastases were detected in 41 (68.3%) patients, including 19 (46.3%) multiple metastases. In statistical analysis, no significant relationship was found between OS and tumor size and the presence of extracranial metastases (p=0.704 and p=0.609, respectively).

Among the laboratory parameters measured at the time of diagnosis, 55% (22/40) of the patients had a CEA level of >5.6 ng/mL, 63% (33/53) of them had high LDH levels (>225 IU/L), 80.7% (46/57) of them had an albumin level of ≤4.34 g/dL, and 27.3% (15/55) of them had hyponatremia. Relationship between OS and clinicopathological features and laboratory parameters is shown in Table 2. In statistical analysis, no significant correlation was found between CEA, LDH, albumin, hyponatremia and survival (p=0.393, p=0.165, p=0.227, and p=0.362, respectively). Median LDH level was 273 (range, 206.5-388.3) IU/L. No significant rela-

tionship was found between LDH level and CEA level, tumor stage, and the presence of brain metastasis at diagnosis (p=1.000, p=0.052, and p=0.329, respectively). Patients with extracranial metastases had a significantly higher LDH level compared to patients without (p=0.027). However, no significant correlation was found between CEA level and the presence of extracranial metastases and tumor stage (p=0.812 and p=1.000, respectively).

Table 2. Factors affecting overall survival*

Variables	Univariate Analysis HR (95% CI)	p	Multivariate Analysis HR (95% CI)	p
Age (years)				
≤60/>60	0.653 (0.286-1.494)	0.313		
Gender				
Female/male	0.782 (0.231-2.644)	0.692		
Smoking history				
Yes/no	0.745 (0.292-1.902)	0.539		
ECOG-PS				
≥2/0–1	2.119 (0.738-6.080)	0.163		
Stage at first diagnosis				
Extensive/Limited	1.649 (0.672-4.044)	0.274		
Tumor size				
Primary tumor >7 cm	0.828 (0.335-2.048)	0.683		
Brain metastasis at diagnosis				
Yes/No	1.734 (0.675-4.454)	0.253		
Presence of brain metastasis				
Yes/No	0.835 (0.329-2.123)	0.706		
Location of brain metastasis				
Supratentorial/Infratentorial	2.325 (0.259-20.839)	0.451		
Number of brain metastases				
>1/1	4.278 (0.475-38.523)	0.195		
Size of brain metastasis				
≥2,5/<2.5cm	4.835 (0.557-41.947)	0.153		
Extracranial metastasis				
Yes/No	1.240 (0.520-2.953)	0.628		
Comorbidities				
Yes/No	2.301 (0.899-5.887)	0.082		
CEA				
>5.6/≤5.6	1.565 (0.507-4.836)	0.436		
Albumin				
>4.34/≤4.34	0.387 (0.089-1.678)	0.205		
LDH				
High/Normal	1.928 (0.697-5.330)	0.206		
Whole-brain Radiotherapy				
No/Yes	10.063 (2.304-43.958)	0.002	28.417 (3.397-237.744)	0.002
Hyponatremia				
Yes/No	1.647 (0.566-4.791)	0.360		
Weight loss				
Yes/No	0.708 (0.086-5.856)	0.748		
Chemotherapy cycles				
<4/≥4	6.946 (2.713-17.782)	<0.001	10.384 (3.281-32.866)	<0.001
Thoracic RT				
No/Yes	7.507 (1.715-32.858)	0.007		
Disease control				
No/Yes	3.043 (1.088-8.512)	0.034		

*Cox Regression Analysis. ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CEA: Carcinoembryonic antigen; LDH: Lactate dehydrogenase; RT: Radiotherapy.

Whole-brain radiotherapy was administered in 40.1% (23/56) and thoracic radiotherapy was applied to the primary tumor in 33.3% (18/54) of the patients. Of these 23 patients, 11 (47.9%) patients received prophylactic cranial radiotherapy, 3 (13%) patients received radiotherapy after brain surgery, and 9 (39.1%) patients received radiotherapy for active brain metastasis. Radiotherapy could not be administered in 5 patients with brain metastasis due to their short survival time after brain metastasis, among whom 4 patients were detected with brain metastases at the time of diagnosis. The DS-GPA score was administered to 13 (76.4%) patients with brain metastases and it was found to be 0-1 in 54.5% (6/13), 1.5-2 in 36.4% (4/13), and ≥2.5 in 9.1% (1/3) of the patients. In patients with brain metastases, mortality was more common in patients with a DS-GPA score of ≤1.5. On the other hand, OS was better in all patients who received whole-brain radiotherapy and those who received thoracic radiotherapy (p=0.002 and p=0.007, respectively).

In terms of systemic treatment, 80.7% (46/57) of the patients received ≥4 cycles of chemotherapy. More than half of the patients (56.6%; 30/54) had primary disease control and it was observed that the rate of primary disease control increased as the number of chemotherapy cycles increased (p<0.001). It was also noted that patients who received ≥4 cycles of chemotherapy had better survival (p<0.001).

Mean OS was 13 (range, 6.2-19.8) months and mean PFS was 8 (range, 2.4-13.6) months. Moreover, the six-month survival rate was 62.1%, the one-year survival rate was 52.1%, and the two-year survival rate was 32.4%. OS and PFS graphs are shown in Figure 1 and 2. In univariate analysis, PFS was found to be affected by all cranial radiotherapy, the number of chemotherapy and disease control (p=0.026, p=0.004 and p=0.001, respectively), while OS was positively affected by the number of chemotherapy cycles, whole-brain radiotherapy, thoracic radiotherapy and disease control (p=0.001, p=0.002, p=0.007 and p=0.034, respectively). In multivariate analysis, however, only the number of chemotherapy cycles and whole-brain radiotherapy were found to affect OS (p<0.001 and p=0.002, respectively).

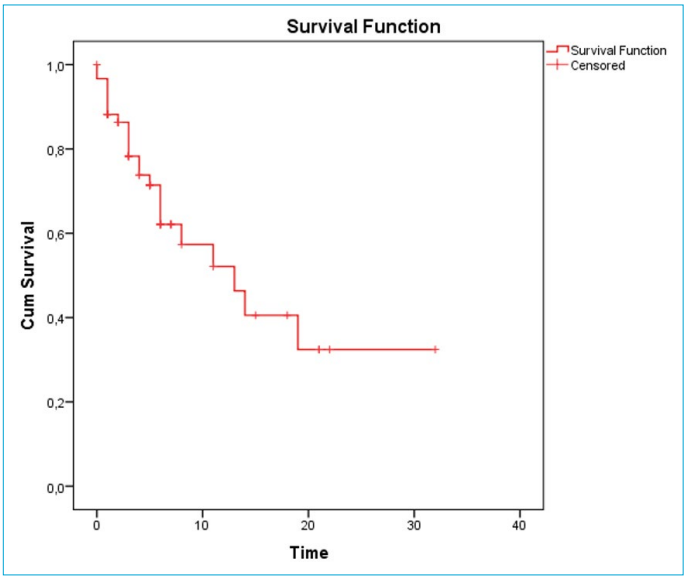

Figure 1. Overall survival.

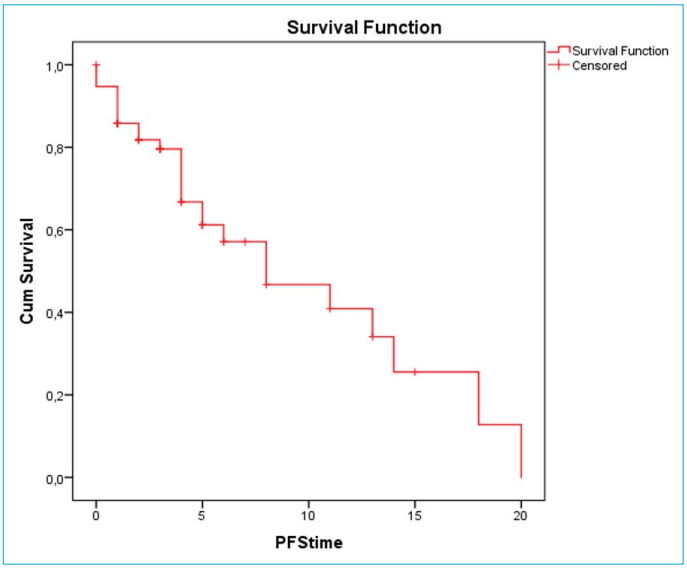

Figure 2. Progression-free survival.

Discussion

The present study was a single-center study and evaluated the effects of clinical, demographic, laboratory parameters and treatment on limited- and extensive-stage SCLC. Our study mostly included patients with high tumor burden and extensive-stage SCLC. Accordingly, it was observed that the factors affecting survival were associated with treatment continuity and disease control rather than demographic, clinical, and tumor characteristics of the patients.

Small-cell lung cancer (SCLC), is likely to develop early and widely disseminated hematogenous metastasis due to its rapid doubling time and rapid growth fraction. Smoking is the primary risk factor for SCLC development, though its incidence has been decreasing recently. Although SCLC was previously more common in men, its incidence has recently increased in women.[11,12] In our study, the patients smoked a median of 40 (range, 11.3-60) packs/year and the male-to-female ratio was 5:1. These findings could be associated with the fact that men smoke more intensely and frequently than women, in our region. On the other hand, the frequency of SCLC in Turkey is decreasing due to the

reduction in the prevalence of smoking, which is a result of the smoking cessation policies and the widespread smoking bans implemented in indoor areas.

Most important prognostic factors for SCLC development are known to include advanced disease stage, poor performance status, and high serum LDH levels.[2,10,13] In our study, 66.7% of the patients had extensive-stage SCLC and 61.2% of them had an ECOG performance status of ≥2. Additionally, median LDH level (273 IU/L) was found to be above the normal range. Although most of our patients had extensive-stage SCLC, their tumor and patient characteristics did not affect the survival. On the other hand, although our survival times were similar to those reported in the literature. This suggests that the reason why we could not reach statistical significance is related to the limited number of patients and our evaluation of a heterogeneous group, which includes limited and extensive stage patients.

Lactate dehydrogenase (LDH) is an important enzyme found in many living tissues in the body and is an indicator of tissue damage. Many cancers are known to cause increased LDH levels. However, LDH is not considered a reliable tumor marker since LDH level can be affected by numerous factors. Of note, high LDH levels can be observed particularly in conditions such as heart failure, hypothyroidism, anemia, meningitis, encephalitis, acute pancreatitis, HIV, and lung or liver disease.[14] Anami et al. showed that high LDH levels can provide valuable information for the identification of patients with brain metastases that may have poor survival.[10] In our study, high LDH levels were detected in 63% of the patients at diagnosis, most of whom included patients with extracranial metastases (p=0.027). However, no relationship was found between LDH level and brain metastasis and survival, which could be associated with the high tumor burden in the majority of our patients and the low number of patients with brain metastases.

Studies have reported that 13-15.5% of patients are detected with solitary brain metastases at the time of diagnosis and 40-50% of patients develop brain metastases during the time from diagnosis to death.[3,15] In a previous meta-analysis, Reddy et al. reported that the mean size of primary tumor was >7 cm and also noted that synchronous and bone metastases, male gender, young age, and American Indians/Alaska native and black patients were predictive factors for increased frequency of solitary brain metastasis[4]. In our study, 88.2% of patients with brain metastases were in the extensive stage at the time of diagnosis. However, due to the limited number of patients and high tumor burden, no significant relationship was found between brain metastasis and age, gender, tumor size, and extracranial metastasis and also no significant relationship was found between patients with and without brain metastasis with regard to survival.

Advancements in treatment and the emergence of techniques such as whole-brain radiotherapy and stereotactic radiosurgery have improved the control of brain metastases.[16,17] In our study, three patients with brain metastases underwent surgical treatment, followed by cranial radiotherapy. Additionally, whole-brain radiotherapy could be applied only in 12 out of 17 patients with brain metastases and the remaining 5 patients died due to rapid progression. On the other hand, mean GPA score was administered to 13 patients with brain metastases and the prognosis of patients with a GPA score of ≤1.5 was worse compared to patients with a higher score. However, due to the small number of patients, statistical significance could not be obtained. In our center, which has a single radiotherapy device, the standard approach is administered in patients with brain metastases. Since the aim of our study was not to evaluate the effects of other radiotherapy techniques on survival, only patients who received whole-brain radiotherapy were included in the study. Our findings indicated that survival was significantly affected in patients who received whole-brain radiotherapy and in those whose brain metastases were controlled (p=0.002).

Carcinoembryonic antigen (CEA) is a glycoprotein used as a tumor marker in gastrointestinal cancers, breast cancer, and SCLC. Tumor cell adhesion has been associated with immunological defense and cell survival and is also considered to potentially predict the risk of brain metastasis thanks to its ability to cross the blood-brain barrier and to form high vascular tumoral cell adhesion.[6] Elevated serum CEA levels, particularly after prophylactic cranial radiotherapy, have been associated with poor prognosis.[8] Guo et al. showed that CEA may be a predictive marker in the development of brain metastases in SCLC.[6] Although high CEA level has been found to be a determinant of PFS and OS in non-small cell lung cancer, this finding has not been demonstrated in SCLC.[18,19] In our center, as recommended in the guidelines, CEA levels were not studied in patients diagnosed with SCLC. However, in patients who presented to our outpatient clinic with symptoms of lung mass and were primarily suspected with non-small cell lung cancer but were later found to have SCLC, the CEA levels measured at the time of first admission were evaluated. On the other hand, although most of our patients had a high tumor burden, CEA level was found to be >5.6 in only 45% of the patients, which was consistent with the literature.[7,8] Nevertheless, the relationship between CEA level and survival could not be demonstrated in our study and thus we suggest that CEA level should not be used as a tumor marker in SCLC.

Paraneoplastic syndromes can occur even years before the emergence of primary tumors. Hyponatremia is a paraneoplastic syndrome resulting from inappropriate antidiuretic hormone (ADH) release in SCLC.[20] It is also the most common electrolyte disorder in cancer patients and studies have shown that persistent hyponatremia despite treatment has adverse effects on survival in SCLC.[20-22] In our study, hyponatremia was detected in approximately one quarter of our patients, while no significant relationship was found between hyponatremia and tumor stage, presence of brain metastases, presence of extracranial metastases, and survival. In addition to, the course of hyponatremia and the presence of treatment-refractory hyponatremia could not be demonstrated, which could be the reason for the absence of a significant difference between patients with and without hyponatremia with regard to survival.

Malnutrition and cachexia are significant problems seen in cancer patients, both of which may result from the disease or the treatment. Weight loss and hypoalbuminemia are among the parameters used for evaluating nutritional status.[23,24] In SCLS, as in other cancers, low albumin levels have been associated with a poor prognosis.[23] In our study, although hypoalbuminemia was detected in 80.7% of the patients, significant weight loss was not observed in any patient due to the rapidly progressing disease. Additionally, no relationship was found between nutritional parameters and survival, which could be attributed to the limited number of patients and the inclusion of a heterogeneous (limited/extensive stage) patient group.

Small-cell lung cancer (SCLC) is a malignancy requiring prompt treatment and disease control. The median survival for extensive-stage SCLC is less than one year. In sensitive tumors, chemotherapy and radiotherapy improve the treatment response, disease control, and survival.[25] In our study, median survival was 13 months and disease control was observed in 56.6% of the patients. In line with the literature, the rate of disease control was better and survival was positively affected in patients who received systemic therapy for a longer period of time.

The strength of our study was that it consisted of patients who were followed up in a single oncological research center and were treated with the standard treatment approach and standard laboratory reference values. Additionally, the evaluation of treatment response was performed in the same way for all patients and the management of side effects was conducted using similar approaches. Nevertheless, our study was limited since it had a limited number of patients, evaluated limited- and extensive-stage patients together, and did not evaluate the levels of laboratory parameters (CEA, LDH, albumin, sodium) during the treatment process.

Conclusion

Small-cell lung cancer (SCLC) is losing its popularity in oncological studies due to its aggressive course and the scarcity of targeted therapies. Although the treatment is sensitive, knowledge of factors affecting survival in SCLC is of prime importance due to the short relapse interval of the disease. Our findings indicated that long-term systemic therapy and cranial and thoracic radiotherapy are significant factors affecting survival. We consider that the success of systemic treatment is the most important factor affecting survival and that further comprehensive studies are needed on this subject.

Disclosures

Ethics Committee Approval: The study protocol was approved by Bursa City Hospital Ethics Committee (Approval Date: 11.08.2021; No: 2021-1419).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – E.K., A.U.; Design – E.K.; Supervision – E.K.; Data collection &/or processing – E.K., A.U.; Analysis and/or interpretation – E.K., A.U., S.K.; Literature search – E.K.; Writing – E.K., A.U.; Critical review – E.K., S.K.

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