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Original Article

Retrospective Analysis of Prognostic Factors in Patients with Small Cell Lung Cancer

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ABSTRACT

Background: The goal of this study is to examine how small cell lung cancer (SCLC) prognosis and survival are impacted by pre-treatment clinical characteristics and laboratory data.

Material and Method: The 118 patients diagnosed with SCLC in our center between August 2000 and December 2008 were evaluated retrospectively. The effects of the 19 variables [hemoglobin (Hgb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin, sedimentation, sodium (Na), neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), alpha-fetoprotein (AFP), performance status (PS), stage, sex, weight loss, age, smoking, chemotherapy (CT) related to the prognosis on survival were thoroughly investigated in detail. Statistically, univariate analyses were performed via Kaplan-Meier Method and multivariate analyses were performed via the Cox proportional hazards (Cox PH) model. The covariates that were found to have a significant relation ($p<0.05$) on prognosis in univariate analyses and the ones with $p<0.15$ in the univariate analyses were subjected to multivariate analysis to determine independent prognostic factors.

Results: In univariate analyses, albumin, Na, NSE, CA 125, stage, and sex had a significant relation to prognosis ($p<0.05$). In multivariate analyses, only the stage parameter was found to be an independent predictive factor on prognosis ($p=0.019$).

Conclusion: The knowledge of prognostic factors like the laboratory and clinical parameters and staging of the patients were considered to have a directing role in determining treatment strategies and clinical follow-up in SCLC.

Keywords: Small cell lung cancer, prognostic factors, survival, lung cancer

INTRODUCTION

The leading cause of cancer-related death worldwide is lung cancer (1). Small cell lung cancer (SCLC) is regarded as a distinct entity from non-small cell lung cancer (NSCLC) due to its being observed mostly in smokers, its rapid growth, and the development of early metastases. SCLC, which constitutes 15-25% of lung cancer cases, is characterized by rapid dissemination, early metastasis, low survival rate, and short mean survival (2). At the time of diagnosis, approximately two-thirds of patients with SCLC are in the extensive stage, and one-third are in the limited stage (3). Compared to other lung cancers, SCLC has a worse prognosis and lower survival rates.

Typically, SCLC patients do not consult a physician until their symptoms worsen and become evident. At the time of diagnosis, most SCLC patients are in the extensive stage. Staging determines prognosis and treatment. The operation plays a minor role in the treatment of the disease. Less than 10% of patients with the lung-confined disease are candidates for thoracotomy. In staging, the Veterans' Administration Lung Study Group (VALSG) uses a simpler two-stage system instead of the tumor-node-metastasis (TNM) staging system that is used in most types of cancer (4). In the VALSG system, the limited stage is defined as the disease being limited to

a hemithorax containing the "tolerable" radiation area. All other patients are considered to be at the extensive stage of the disease. The distinction between the limited and the extensive stage is important since patients with limited stages can benefit from the combined treatment regimen.

Knowing a number of prognostic factors at the time of diagnosis is important in predicting the clinical outcome in cancers such as SCLC, which have an aggressive course and have a very low long-term survival rate. In addition, knowing some predictive factors that will determine the treatment toxicity and the response to treatment is crucial for patient selection and estimating treatment response.

MATERIALS AND METHODS

Study Design and Data Source

In our retrospective observational analytical study, the 118 patients diagnosed with SCLC in the Medical Oncology Clinic of our center between August 2000 and December 2008 were analyzed retrospectively in order to investigate whether pre-treatment clinical features and laboratory parameters have an effect on prognosis and survival. The data of the variables being examined was obtained from the medical records. The follow-up period started on 01.08.2000, the first diagnostic data of the 118 patients; It terminated on 16.11.2009, covering the date of the last exitus case noted in this group (15.11.2009). A statistical study was performed on the 19 covariates that were deemed to be related to prognosis. The 6 covariates that were found to have a significant relation ($p<0.05$) on prognosis plus the 4 covariates with $p<0.15$ in univariate analyses were taken to multivariate analysis in order to determine independent prognostic factors. The variables deemed to be related to prognosis and survival are shown in **Table 1**.

STATISTICAL ANALYSIS

The Predictive Analytics Software Statistics 18 (PASW Statistics 18) package program was used to conduct the statistical analysis. To compare the groups as pairs, we employed the Mann-Whitney U test.

For survival analysis, univariate statistical analyses were performed using the Kaplan-Meier method; logrank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware tests were used to examine the effects of a total of 19 covariates on prognosis.The variables that were found to have an eligible relation on survival (i.e., significance with $p<0.15$) by the Kaplan-Meier method in univariate statistical analyses were added to the multivariate model as candidate risk factors. Multivariate regression analyses were realized via the Cox PH model. The 95% confidence intervals of the variables were calculated. All tests were performed with a 95% confidence interval. All results with $p<0.05$ were considered statistically significant.

Table 1. Prognostic factors for survival

Category of variable	#	Covariates
Hemogram	1	Hgb
Biochemistry	2	LDH
	3	ALP
	4	Albumin
	5	Na
Sedimentation	6	Sedimentation
Tumor Markers	7	NSE
	8	CEA
	9	CA 15-3
	10	CA 125
	11	CA 19-9
	12	AFP
Other	13	Performance status
	14	Stage
	15	Sex
	16	Weight loss
	17	Age
	18	Smoking
	19	CT

Hgb; hemoglobin, LDH; lactate dehidrogenase, ALP; alkaline phosphatase, Na; sodium, NSE; neuron-specific enolase, CEA; carcinoembryonic antigen, CA; cancer antigen, AFP; alpha-fetoprotein, CT; chemotherapy

RESULTS

The mean age of 118 patients was 55.98±11.83 years (min:29.97, max:82.00). Out of 118 patients, 38 (84%) of 45 elderly patients (≥60 years old) and 54 (74%) of 73 patients (<60 years old) were found to be exitus in the follow-up period. The mean survival of elderly patients was 15.17±2.77 months, and the mean survival of other patients was 19.84±2.01 months (mean survival of 118 patients: 18.80±1.90 months). No significant effect of the age variable on survival was observed ($p=0.053$); however, the Breslow and Tarone-Ware tests gave statistically significant results ($p=0.040$ and 0.037). Of the 118 patients, 106 (89.8%) were male and 12 (10.2%) were female. The mean survival time was 16.92±1.84 months in male patients and 33.86±5.34 months in female patients, and the sex covariate was found to be significant on survival ($p=0.004$).

Among 118 patients, 19 (68%) of 28 with weight loss died, and 73 (81%) of 90 without weight loss died. The mean survival of those with weight loss was 23.19±5.13 months, and those without weight loss were 17.06±1.57 months. There was no significant effect of weight loss on survival ($p=0.645$).

Smoking history data of 116 (98.3%) of 118 patients were obtained. Those who had been exposed to cigarettes (current smokers and those who have quit) and those who had not been exposed (never smoked)

were analyzed in the variable "smoking exposure". When the survival data were handled separately with the variables "smoking exposure" and "smoking (during diagnosis)" as the only variable via the Kaplan-Meier model, no significant difference was found according to the logrank (Mantel-Cox) test (p=0.674 and 0.333, respectively). Mean survival time was observed to be 18.24±2.06 months in smokers (95% confidence interval: 14.15–22.20 months), and 20.75±3.84 months in non-smokers (95% confidence interval: 13.18–28.19 months).

Staging data were available for 114 of the 118 patients; 79 (66.9%) were in the extensive stage and 35 (29.7%) were in the limited stage. The mean survival time was found to be 26.91±4.39 months in limited-stage patients and 14.81±1.60 months in extensive stage patients. This difference was statistically significant (p=0.016). The disease being in the extensive stage was found to be a bad prognostic factor. The stage was found to be an independent prognostic factor in both uni-covariate Kaplan-Meier model analyses and multi-covariate Cox PH model analyses (p=0.016 and p=0.019, respectively). Differences in laboratory findings between stages were also evaluated, and a significant difference was observed between stages in ALP and CEA parameters (p=0.011, p=0.016, respectively). The values determined in the stage comparisons and p values are shown in **Table 2**.

As for chemotherapy (CT), the patients were divided into two groups: those treated with Etoposide-Cisplatin (EP) and those treated with other chemotherapeutic agents. Of 118 patients, 102 (86.4%) received CT, and 16 did not. Of the patients who received CT, 69 (77%) of 90 (88.24%) were treated with EP, and 9 (75%) of 12 (11.76%) were treated with other chemotherapeutic agents died. Mean survival in patients treated with EP and other agents was 19.76±2.10 months and 11.47±3.83 months, respectively. In CT, there was no significant difference between EP and treatment with other agents (p=0.129). When the patients who received CT and those who did not receive CT were compared, the following data were obtained: Mean survival in patients who did not receive CT was 13.88±3.76 months, and in patients who received CT, it was 18.99±1.99 months; no significant difference was found between receiving and not receiving CT (p=0.407).

Performance status (PS) was determined by the Eastern Cooperative Oncology Group (ECOG) scale, and patients with ECOG 0 and 1 according to their PS were compared with those with ECOG 2, 3, and 4 using the Kaplan-Meier model. Of 118 patients, 60 (51%) had ECOG>1, and 58 (49%) had ECOG≤1. Mean survival time was 19.75±2.26 months (95% confidence interval: 15.28–24.09 months) in ECOG≤1 patients, and 16.19±2.31 months (95% confidence interval: 11.62-20.65 months) in ECOG>1 patients, and no statistically significant difference was observed between the two groups (logrank, Breslow, Tarone-Ware tests: p=0.132, p=0.108, and p=0.111, respectively). Although the p values were not less than the default 0.05 level, we noted all were less than 0.14. PS could not be demonstrated as an independent prognostic factor with multivariate analyzes (Cox PH, Wald: p=0.839).

The laboratory data revealed the followings: The mean survival of patients with normal Hgb levels and those with low Hgb levels were 17.23±2.04 months and 19.37±2.55 months, respectively. There was no significant effect of

Table 2. Comparison of limited and extensive stage laboratory values

Category of variable	Covariate	Unit	Limited + Extensive	Limited Stage	Extensive Stage	p value
Hemogram	Hgb	g/dL		Normal:12 Low:22	Normal:27 Low:52	0.909
Biochemistry	LDH	U/L		Normal:15 High:19	Normal:21 High:55	0.090
	ALP	U/L		Normal:27 High:7	Normal:42 High:36	**0.011**
	Albumin	g/dl		Normal:30 Low:4	Normal:57 Low:21	0.078
	Na	mEq/L	138.7±3.2	139.0±2.7	138.7±3.5	0.492
Sedimentation	Sedimentation	mm/h	49.3±28.7	48.7±27.8	50.9±29.9	0.894
Tumor Markers	NSE	mcg/L	42.4±65.9	25.0±20.6	48.4±75.2	0.257
	CEA	ng/ml	62.0±153.9	2.7±0.8	78.3±170.9	**0.016**
	CA 15-3	IU/ml	45.6±85.7	14.5±0.3	46.8±93.5	0.112
	CA 125	IU/ml	47.8±47.4	17.8±5.3	58.2±50.9	0.083
	CA 19-9	IU/ml	395.5±1376.0	72.3±94.4	497.2±1575.1	0.823
	AFP	ng/ml	4.6±6.9	4.4±3.9	4.7±7.5	0.895

Hgb level on survival (p=0.918). The mean survival of patients with normal LDH levels and those with high LDH were 20.11±2.50 months and 16.95±2.27 months, respectively. There was no significant effect of LDH level on survival (p=0.134). There was no significant difference between limited and extensive stages in terms of LDH (Mann-Whitney U; p=0.090). The mean survival of patients with normal ALP levels and those with high ALP were 21.40±2.61 months and 13.85±2.11 months, respectively. There was no significant effect of ALP level on survival (p=0.077) (**Table 3**). Here, we noted the margin of the rejection level the significance. Out of 91 (of 116) patients with normal albumin, 70 (77%) died. Of the 25 with low albumin, 21 (84%) died. The mean survival of patients with normal albumin levels and those with low albumin were 18.97±1.71 months and 11.53±3.28 months, respectively. A very significant effect of albumin level on survival was found (p=0.008). Out of 105 (of 115) patients with normal Na, 80 (76%) died. 9 out of 10 (90%) with low Na died. The mean survival of patients with normal Na levels and those with low Na were 19.05±1.95 months and 11.05±5.90 months, respectively. A significant effect of Na level on survival was found (p=0.046). The mean survival of the patients with normal sediment and those with high sedimentation were 8.19±3.27 months and 20.41±2.53 months, respectively. No significant effect of sedimentation on survival was found (p=0.178).

As for tumor markers: Of the 27 patients whose NSE was analyzed; 3 (60%) of the 5 with normal NSE died and 16 (73%) of the 22 with high NSE died. The mean survival of patients with normal NSE levels and those with high NSE were 40.13±5.83 months and 16.65±3.23 months, respectively. A very significant effect of NSE level on survival was found (p=0.033). The mean survival of patients with normal CEA levels and those with high CEA were 21.66±6.25 months and 14.57±2.82 months, respectively. There was no significant effect of

Table 3. The relationship between the clinical and laboratory findings and the survival

Category of variable	Covariates	Unit	Control values	Mean Survival (months) <with K-M>	p value (1 covariate) <Kaplan-Meier>	p value (>1 covariates)<Cox PH>
Hemogram	Hgb	g/dL	>12 <12	17.29±2.05 19.44±2.55	0.918	
Biochemistry	LDH	U/L	Normal≤192 High>192	20.18±2.51 17.01±2.28	0.134[b]	
	ALP	U/L	Normal≤106 High>106	21.47±2.62 13.89±2.12	0.077[b]	
	Albumin	g/dl	Low≤3.5 Normal>3.5	19.04±1.72 11.57±3.30	**0.008**[a]	
	Sedimentation	mm/h	Normal≤12 High>12	8.22±3.29 20.48±2.54	0.178	
	Na	mEq/L	Normal:≥135 Low:<135	19.11±1.95 11.09±5.92	**0.046**[a]	
Tumor Markers	NSE	mcg/L	Normal:<12.5 High: >12.5	40.27±5.85 16.71±3.24	**0.033**[a]	
	CEA	ng/ml	Normal: <3 High: >3	21.73±6.27 14.62±2.82	0.194	
	CA 15-3	IU/ml	Normal: <31 High: >31	20.63±4.49 11.76±4.92	0.263	
	CA 125	IU/ml	Normal: ≤35 High: >35	25.68±5.28 9.43±2.55	**0.037**[a]	
	CA 19-9	IU/ml	Normal: <37 High: >37	17.59±3.78 14.68±4.62	0.766	
	AFP	ng/ml	Normal: <9 High: >9	11.64±2.21 5.44±0	0.532	
Other	PS		ECOG0-1 ECOG2-3-4	19.75±2.26 16.19±2.31	0.132[b]	
	Stage		Limited Extensive	26.91±4.39 14.81±1.59	**0.016**[a]	**0.019**
	Sex		Male Female	16.92±1.84 33.86±5.34	**0.004**[a]	
	Weight loss, kg		Yes No	23.27±5.15 17.12±1.58	0.645	
	Age, year		Other: <60 Elderly: >60	19.91±2.01 15.22±2.78	0.053[b]	
	Smoking		Yes No	18.24±2.06 20.75±3.84	0.333	
	CT-receiving		Yes No	18.99±1.99 13.88±3.76	0.407	

[a]: Significant at the default 0.05 level; Candidate covariate to be used in the Cox PH model.

[b]: Significant at the 0.15 level; Candidate covariate to be used in the Cox PH model.

CEA level on survival (p=0.194). The mean survival of patients with normal CA 15-3 and those with high CA 15-3 were 20.56±4.48 months and 11.72±4.91 months, respectively. There was no significant effect of CA 15-3 level on survival (p=0.263). The mean survival of patients with normal CA 125 and those with high CA 125 were 25.59±5.26 months and 9.40±2.54 months, respectively. A significant effect of the CA 125 level on survival was found (p=0.037). The mean survival of patients with normal CA 19-9 and those with high CA 19-9 were 17.53±3.76 months and 14.63±4.61 months. There was no significant effect of CA 19-9 level on survival (logrank, Breslow, Tarone-Ware tests: p=0.766, p=0.327, and p=0.476, respectively). The mean survival of patients with normal AFP levels and those with high AFP were 11.60±2.20 months and 5.42±0.00 months, respectively. There was no significant effect of AFP level on survival (p=0.532).

DISCUSSION

At the time of diagnosis, approximately 2/3 of the patients with SCLC are in the extensive stage and 1/3 are in the limited stage (3). The scattering of patients in our study is also in this direction: 79 (66.9%) of 118 patients were diagnosed in extensive stage and 39 (33.1%) in limited stage. In patients with extensive stage SCLC, all metastatic localizations especially liver, brain, bone marrow, and bone have prognostic importance. The absence of brain and liver involvement stage and the presence of a single metastatic focus in the extensive stage are indicators of better prognosis (5). In our study, out of the 83 patients with extensive stage, 21 of 26 patients with a single metastatic focus died, and 49 of 57 patients with multiple metastases died. The mean survival of patients with a single metastatic focus and those with multiple metastatic sites were 15.33±3.31 months and 13.53±1.50 months, respectively. However, there was no significant relation of the number of metastases on survival. In our study, the most common sites of metastasis were liver (53.8%), bone (37.2%), ipsilateral pleural effusion (32.1%), and central nervous system (24.4%). In our study, the mean survival time was observed as 26.91±4.39 months in the limited stage patients and 14.81±1.60 months in the extensive stage patients, with a significantly longer mean survival in the limited stage patients. In multivariate analyses, stage was found to be an independent prognostic factor.

The effect of age on survival in SCLC is controversial. In the study of Yuen et al., in patients aged 70 years and older, the response and survival rates to combined therapy were similar to younger patients, but toxicity was higher than that of the young (6). Advanced age has been associated with lower PS and more comorbid diseases, often requiring dose adjustment in combination chemotherapy (7). As for our study, the mean survival time of patients under the age of 60 was 19.91±2.01 months, and the mean survival time of patients aged 60 and over was 15.22±2.78 months. Although the relationship of age with prognosis was not statistically significant, the rejection of significance was made with a very small margin which means there is clinical significance.

Female sex has been associated with better response and survival in SCLC (8). The exact reason why women respond better than men is unknown. IIn our study, female patients' mean survival was better than male patients, consistent with the literature.

Wet et al. showed that weight loss is an important variable in prognosis. In that study, there was no difference in average survival between patients without weight loss and those with <10% weight loss, but it was concluded that weight loss was a bad prognostic factor in patients with >10% weight loss (9). In our study, however, no significant relationship was found between weight loss and survival (p=0.645).

The most important known cause of SCLC is smoking, which is detected in approximately 95% of cases (10). Continuing to smoking is a bad prognostic factor. Smokers have more side effects from CT treatment. Smoking increases the morbidity and mortality rates in patients with concomitant COPD and coronary artery disease. Smoking cessation can prolong survival and reduce the risk of relapse (11). In our study, the mean survival of non-smokers was 20.75±3.84 months, and the mean survival of smokers was 18.24±2.06 months. However, the relationship between smoking and survival was not significant.

Rawson et al. reported that PS, serum ALP level, and the disease stage were the most important prognostic factors in a multicenter study conducted with 3873 patients (12). In our study, patients with ECOG 0 and 1 according to PS were compared with those with ECOG 2, 3 and 4. In the univariate analysis, the mean survival time was 19.75±2.26 months in patients with ECOG≤1 and 16.19±2.31 months in patients with ECOG>1, and no statistically significant difference was observed. Here, we noted the margin of the rejection level of the significance. PS could not be shown as an independent prognostic factor with multivariate analyses.

Because SCLC is chemosensitive, its treatment should be started as soon as the diagnosis is made, regardless of the stage. Patients who respond well to CT have a better prognosis. Patients with early relapse after CT have a low chance of responding to second-line therapy and have a bad prognosis. In our study, the mean survival was found to be 18.99±1.99 months in patients receiving CT, and 13.88±3.76 months in patients not receiving CT (13). No significant relation was found

between receiving CT and survival, however, the fact that the mean survival of patients who received CT was clearly higher than the mean survival of patients who did not receive CT, it shows that if the study included more cases, a significant relationship may possibly be obtained, which is consistent with the literature.

The increase in the laboratory parameter LDH was detected in 33%-57% of all SCLC patients and 85% of extensive stage patients, and is a strong predictive and prognostic factor. Increased LDH level is associated with bone marrow involvement. It has been claimed that LDH measurement alone can be used instead of routine bone marrow application because it is a cheap and quick test. In our study, however, no significant difference was found between limited and extensive stages in terms of LDH. Also, there was no significant effect of LDH level on survival. The effect of serum albumin level on survival in SCLC is controversial. In our study, a significant relation was found between albumin level and survival in univariate analysis. Mean survival was 19.04±1.72 months in patients with normal albumin levels, and 11.57±3.30 months in patients with low albumin levels. Anemia is common in patients with SCLC. Cohen et al. suggested that the hemoglobin value during diagnosis is associated with survival (14). In our study, however, no significant relation was found between hemoglobin level and survival in univariate analysis. In the study of Rawson et al. that included 3873 patients, it was shown that serum ALP level is the most important prognostic factor together with PS and stage (12). Elevated ALP is mostly attributed to liver and bone metastases, which are common in SCLC, and therefore to the extensive stage disease. In our study, although there is no significant relationship of ALP on survival, the significance was denied with a small margin. According to Rawson, serum Na level is also one of the important prognostic factors (12). Similarly, in our study, the relation of Na on survival was significant in univariate analysis.

High levels of NSE, one of the tumor markers, are detected in neuroendocrine cells and neurogenic tumors as well as in the serum of patients with SCLC (15). The level of NSE is found to be high at the time of diagnosis in 80% of SCLC patients and is considered a characteristic tumor marker of SCLC. NSE is higher in untreated patients in the extensive stage than in those in the limited stage. Although it provides information about the extent and prognosis of the disease, it is mostly used in treatment follow-up. In our study, NSE appeared as a significant prognostic factor in univariate analysis. CEA has been found to have a predictive value in the prognosis of SCLC in many series. It has been reported that CEA is increased more in metastatic disease, especially in liver and bone marrow metastases (16). In our study, no significant effect of CEA on prognosis was found. It has been reported that the level of CA 125 may increase in NSCLC rather than SCLC, mostly in adenocarcinoma and large cell lung cancer (17). However, in our study, CA 125 had a significant effect on prognosis.

CONCLUSION

The prognostic value of simple clinical and laboratory parameters before the treatment of SCLC is essential because of the difficulty of detecting small or distant metastases, the expensive, time-consuming, and invasive nature of the staging procedures, and the necessity to start the treatment of SCLC as soon as possible. Eventually, it is known that some clinical and laboratory parameters determine the response to CT, treatment toxicity, and long-term survival. By means of these factors, patients with good prognosis and bad prognosis can be identified and the relevant treatment strategies can be determined. While the aim is to provide long-term survival in patients with good prognosis; it should be to provide maximum palliation with minimum toxicity in those with bad prognosis. Studies on prognostic factors in SCLC are still being conducted, and in the light of these studies, healthier decisions can be made about treatments.

DECLARATIONS

Ethics Committee Approval: Not seeking Institutional Review Board review was in accordance with the policy of Ankara City Hospital since retrospective ethics committee approval is not required for articles that were produced from pre-2020 research data and for doctoral thesis studies.

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Conflict of interest: None.

Informed consent form: Since the study was a retrospective analysis, no consent was required as per the then-regulations.

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