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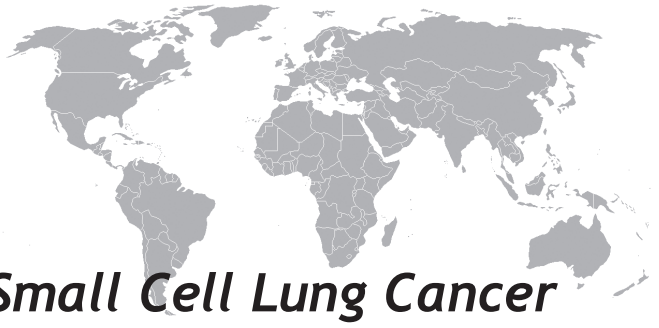

Factors Affecting Survival in Small Cell Lung Cancer

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ABSTRACT

Objective: Small cell lung cancer (SCLC) constitutes about 15-25 % of lung cancers with high mortality rate. Herein we observed the effect of parameters at the time of diagnosis to survival of cases with SCLC.

Methods: We evaluated 65 patients who were followed up in our oncology department retrospectively.

Results: Tumor location and stage at the time of diagnosis, smoking history, accompanying comorbidities, ECOG PS, laboratory parameters and treatments applied in pursuit were evaluated. 3-month survival rate of patients was 75.9%, 50.2% for 6-month, 21.4% for 1 year, and 5.5% for 2 years during follow up. ECOG PS and stage were found statistically significant risk factors in model created to determine overall survival.

Conclusion: Performance score at the time of diagnosis, stage and presence of liver metastasis are identified as prognostic factors for SCLC and of these factors are quite valuable to predict the clinical outcome.

Key words: SCLC; prognostic factors; survival

INTRODUCTION

Lung cancer is one of the primary reasons behind deaths caused by cancer all around the world. Small cell lung cancer (SCLC) comprises 15 to 25 % of all lung cancer cases. SCLC is centrally located for most cases. Among the most common complaints are cough, dyspnea, hemoptysis and pain. Symptoms manifest themselves related to an intrathoracic disease or distant metastases. SCLC has a rapid and destructively progressive course. It is considered a systemic disease since it metastasize to distant organs at the early stage. SCLC often metastasize to brain, bones, liver, adrenal and to the opposite lung (1).

More than 50% of cases with lung cancer are diagnosed after the age of 65 while 30% of them follow the suit around the age of 70. The prevalence of accompanying diseases, various geriatric troubles and nutritional disorders are major problems for cases with lung cancer diagnosed at an advanced age. The current primary therapy options for SCLC include chemotherapy (CT) and radiotherapy (RT). SCLC has a poor prognosis in the long run even though it is responsive to CT (2). Various studies have been carried out in an effort to gain insight into factors with an impact on prognosis for SCLC. It is reported that the stage, the Eastern Cooperative Oncology Group performance score (ECOG PS), gender, age, number of metastases, albumin, and the level of alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and sodium (Na) are all influential on prognosis (3).

This study represents an analysis over ECOP PS, localization, stage, smoking history, accompanying comorbidities, and laboratory parameters including the level of LDH, Na, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and calcium (Ca), prevalence and administered chemotherapies as well as their impacts on survival for 65 cases diagnosed with SCLC by our clinics between 2009 and 2013.

MATERIALS AND METHODS

The study retrospectively evaluated 65 cases with full information who were followed up by the Department of Oncology, Faculty of Medicine in Suleyman Demirel University between 2009 and 2013, and histopathologically diagnosed with SCLC. All the demographic information of the cases, ECOG PS, tumor localization and stages, smoking history, methods of diagnosis, accompanying comorbidities, laboratory parameters (LDH, Na, AST, ALT, Ca) and metastatic sites were documented. For the purpose of post-diagnosis staging, they were tested for Thorax computed tomography (CT), abdominal ultrasonography and/or CT, bone scintigraphy and brain CT and/or MRI. Staging was carried out in line with a method recommended by "the Veterans Administration Lung Cancer Group" (4). For the first line therapy, all of the patients were administered with Platinum (Cisplatin 80 mg/m2/day 1st day or Carboplatin 300 mg/m2/day 1st day) + Etoposide 100 mg/m2; 1-3 day(s) for every 21 days.

SPSS 17.0 for Windows was used for statistical analysis. Descriptive statistics were provided as number and percentage for categorical variables, and as average, standard deviation, minimum and maximum for numeric variables. Independent comparison between two groups was performed through Student-t Test in case numerical variables met the requirement

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of normal distribution, and through Mann Whitney U test when they did not. Inter-group rates of the categorical variables were tested via Chi-Square Analysis. Survival rates were tested through Kaplan Meier Survival analysis. Risk factors were defined by Cox regression analysis through test Forward method. Statistical significance level (alpha) was considered as $p<0.05$.

RESULTS

The study included a total of 65 cases including 64 men and 1 woman with an average diagnostic age of 62.4±9.8 years. 93.8 % of the cases were smokers. Number of Cigarette packs/year average of cases was 52.0±25.4. Among comorbid diseases were Essential Hypertension (EH) (15.4%), Diabetes Mellitus (12.3%), Chronic Obstructive Pulmonary Disease (7.7%), Coronary Artery Disease (3.1%) and others (6.2%). ECOG PS scores of the cases at the time of diagnosis were 6.2%- 0, 30.8%- 1, 32.3% - 2, 23.1% - 3, 7.7% - 4. Cases were diagnosed through bronchoscopy (72.3%), transthoracic biopsy (12.3%) and metastatic biopsy (15.4%). 70.8 % of the cases were at extensive stage. Primary tumor was located on right lung for 58.5% of the cases, and on left lung for 41.5% of cases. 33.8% of the cases suffered from pleural effusion. Among the metastatic sites were liver for 30.8%, bone for 15.4%, brain for 12.3%, and others for 10.8% of cases. 30.8 of the cases were diagnosed with no metastasis. The percentage of Vena cava superior syndrome (VCSS) was 6.2% at the time of diagnosis. Biochemical parameters and treatment percentages of the cases are presented in Table 1.

Table 3: *Showing the percentage distribution of FTM studied among 195 subjects studied*

Demographic Info	**Age at diagnosis Avg.±SD (min-max)**		**62.4±9.8 (45-84)**
	Gender n (%)	Male	64 (98.5)
		Female	1 (1.5)
	Smoking (Pack/year) Avg.±SD (min-max)		52.0±25.4 (0-120)
	Comorbidity	N/A	36 (55.4)
		DM	8 (12.3)
		HT	10 (15.4)
		COPD	5 (7.7)
		CAD	2 (3.1)
		Other	4 (6.2)
At diagnosis	**ECOG PS Avg.±SD (min-max)**		2.0±1.1 (0-4)
	n (%)	0	4 (6.2)
		1	20 (30.8)
		2	21 (32.3)
		3	15 (23.1)
		4	5 (7.7)
	Method of diagnosis	Bronchoscopy	47 (72.3)
		Transthoracic biopsy	8 (12.3)
		Metastatic	10 (15.4)
	Stage	Limited	19 (29.2)
		Extensive	46 (70.8)
	Localization	Right	38 (58.5)
		Left	27 (41.5)
	Pleural effusion		22 (33.8)
	Metastatic sites	N/A	20 (30.8)
		Brain	8 (12.3)
		Liver	20 (30.8)
		Bone	10 (15.4)
		Other (Indicate)	7 (10.8)
	VCSS		4 (6.2)
At diagnosis	**Biochemical tests Avg.±SD (min.-max.)**		
	LDH		647.9±902.4 (128-4568)
	Na		136,1±3,8 (125-143)
	AST		40.1±39.8 (11-228)
	ALT		32.0±34.3 (9-233)
	Albumin		3.6±0.6 (2.1-4.6)
Therapy information	Ca		9.1±0.7 (7.3-11.3)
	CT		46 (70.8)
	RT		37 (56.9)
	1st Line CT	No CT	19 (29.2)
		Cisplatin + Etoposide	42 (64.6)
		Carboplatin + Etoposide	4 (6.2)
	CT cure count Avg.±SD (min.-max.)		3.3±2.7 (0-8)
	2nd Line CT		15 (23.1)
	Average length of follow-up (month) Avg.±SD (min-max)		7.0±8.9 (0-60)

46 of cases were administered with CT for the follow-up period while 19 of them were not. 37 of the cases were administered with RT. For the 1st line therapy, 37 of the cases were administered with cisplatin+etoposide while 4 of them were administered with carboplatin+etoposide. 15 of the cases were administered with 2nd line therapy. All of those without a 1st line therapy and with a 2nd line therapy were cases of exitus (Table 2).

ECOG PS average for the followed cases of exitus at the time of diagnosis, and percentages of the extensive stage were statistically high to a significant extent ($p=0.006$ $p<0.001$). There was a statistically significant difference for metastatic site percentages ($p<0.001$). Cases of exitus had a high percentage of liver metastasis. (Table 2)

Table 2: *Factors affecting mortality*

			Alive	**Exitus**	**p**
			Alive	Exitus	p
Demographic information	Age at diagnosis Avg.±SD		59.2±9.3	63.1±9.9	0.216
	Gender n (%)	Male	12 (100)	52 (98.1)	1.000
		Female	0 (0.0)	1 (1.9)	
	Smoking (Pack/year) Avg.±SD		48.4±31.2	52.9±24.2	0.619
	Comorbidity	N/A	7 (58.3)	29 (54.7)	0.240
		DM	0 (0.0)	8 (15.1)	
		HT	3 (25.0)	7 (13.2)	
		COPD	0 (0.0)	5 (9.4)	
		CAD	0 (0.0)	2 (3.8)	
		Other	2 (16.7)	2 (3.8)	
At diagnosis	ECOG PS Avg.±SD		1.3±1.1	2.1±1.0	0.006
	n (%)	0	2 (16.7)	2 (3.8)	0.014
		1	7 (58.3)	13 (24.5)	
		2	2 (16.7)	19 (35.8)	
		3	0 (0.0)	15 (28.3)	
		4	1 (8.3)	4 (7.5)	
	Method of diagnosis	Bronchoscopy	12 (100)	35 (66.0)	0.068
		Transthoracic biopsy	0 (0.0)	8 (15.1)	
		Metastatic	0 (0.0)	10 (18.9)	
	Stage	Limited	10 (83.3)	9 (17.0)	<0.001
		Extensive	2 (16.7)	44 (83.0)	
	Localization	Right	7 (58.3)	31 (58.5)	0.092
		Left	5 (41.7)	22 (41.5)	
	Pleural effusion	Yes	3 (25.0)	19 (35.8)	0.473
	Metastatic sites	N/A	10 (83.3)	10 (18.9)	<0.001
		Brain	1 (8.3)	7 (13.2)	
		Liver	0 (0.0)	20 (37.7)	
		Bone	1 (8.3)	9 (17.0)	
		Other (Indicate)	0 (0.0)	7 (13.2)	
	VCSS		1 (8.3)	3 (5.7)	0.567
At diagnosis	Biochemical tests Avg.±SD				
	LDH		319.4±187.6	724.3±984.3	0.173
	Na		135.4±3.8	136.3±3.9	0.461
	AST		22.6±4.6	44.0±43.1	0.139
	ALT		20.8±8.2	34.6±37.4	0.520
	Albumin		3.7±0.4	3.6±0.6	0.701
	Ca		9.1±0.5	9.1±0.8	0.853
Therapy information	CT		12 (100)	34 (64.2)	0.014
	RT		9 (75.0)	28 (52.8)	0.161
	1st Line CT	No CT	0 (0.0)	19 (35.8)	0.020
		Cisplatin + Etoposide	11 (91.7)	31 (58.5)	
		Carboplatin + Etoposide	1 (8.3)	3 (5.7)	
	CT cure count Avg.±SD (min.-max.)		4.3±1.8	3.1±2.8	0.133
	2nd Line CT		0 (0.0)	15 (28.3)	0.036
	Average length of follow-up Avg.±SD		11.3±16.0	6.0±6.1	0.151

Average length of follow-up was 7.0±8.9 (min=0 max=60). 81.5 of cases were exitus over the period of follow-up. 78.5% of the exitus were disease-related while 3.1% were non-disease related (Table 3).

Table 3: *Exitus Ratio*

Latest status	Alive	12 (18.5)
	Exitus	53 (81.5)
Cause of exitus	Disease-related	51 (78.5)
	Non-disease related	2 (3.1)

ECOG PS and stage were found to be statistically significant risk factors for the model established in an effort to identify the general survival among age, gender, cigarette pack/year, ECOG PS, stage, localization, pleural effusion, VCSS and comorbidity at the time were diagnosed (Figure 1).

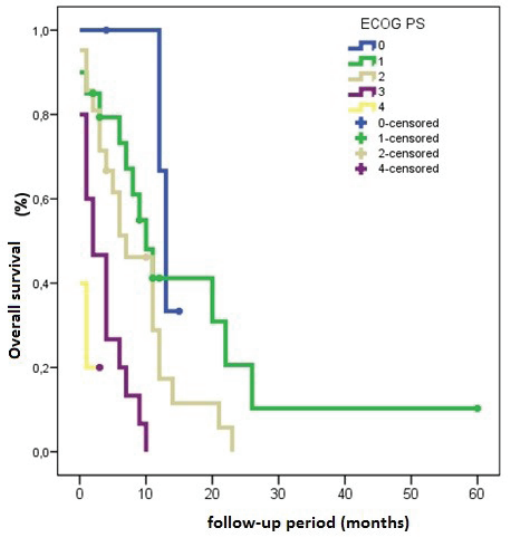

Figure 1: *Overall survival according to ECOG PS*

Estimated median survival times of ECOG PS groups proved a statistically significant difference (p<0.001) (Table 4).

Table 4: *Estimated median survival times of ECOG PS groups*

Estimated overall survival time (month)					
ECOG PS	Median	SEM	95% CI	Log-Rank p	
0	13	0.8	11.4	14.6	<0.001
1	10	1.9	6.3	13.7	
2	7	2.0	3.0	11.0	
3	2	1.2	0.0	4.3	
4	0	.	.	.	

3-month survival percentages of the cases for follow-up were 75.9% while 6-month, 1-year and 2-year percentages were 50.2%, 21.4%, and 5.5% respectively. Estimated median survival time was 7 months (Figure 2, Table 5). Estimated median survival time for the extensive stage was 1.2 months while the median value for the limited stage was 11.6 months. Estimated median survival times of the groups proved a statistically significant difference (p<0.001) (Figure 3, Table 6).

Table 5: *Overall survival*

Estimated overall survival time (month) median±SEM (m%95 CI)		7.0±1.0 (5-9)
Overall survival	3 months	75.9%
	6 months	50.2%
	1 year	21.4%
	2 year	5.5%

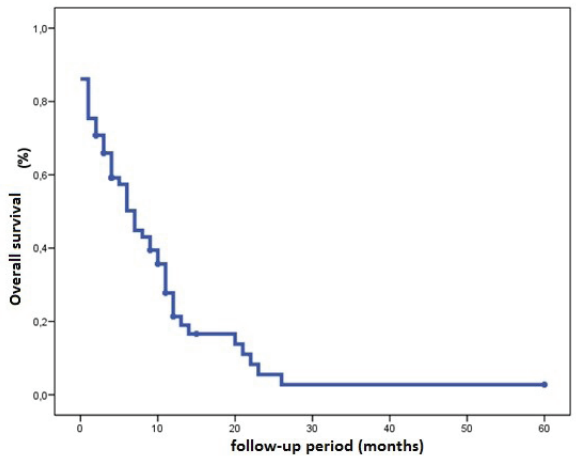

Figure 2: *Overall survival during follow-up*

Table 6: *Estimated overall survival time (month) by stage*

	Estimated overall survival time (month)				
Stage	Median	SEM	95% CI	Log-Rank p	
Limited	22	11.6	0.0	44.8	<0.001
Extensive	4	1.2	1.6	6.4	

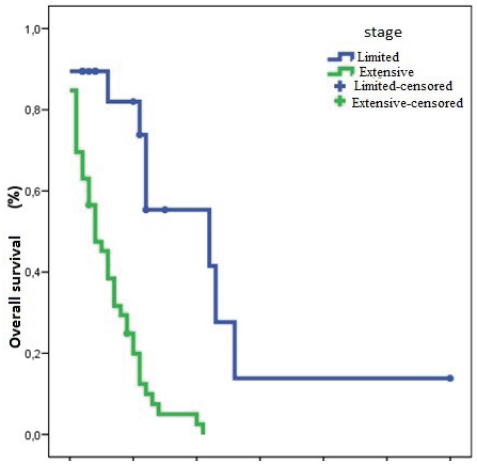

Figure 2: *overall survival time by stage*

DISCUSSION

SCLC is a type of cancer with a highly aggressive course and a low long-term survival rate (5). It is argued that some laboratory parameters at the time of diagnosis can be put into use as prognostic factors for SCLC patients (6). Advanced age, comorbidities that surface with age, and decreased physiological reserve point to a poor prognosis. At the time of diagnosis, about 2/3 of patients are at the extensive stage (7). Retrospectively carried out with 18153 SCLC cases, a study revealed that the median survival time was 6 months for all the patients, 1 year for patients at the limited stage, and 4 months for those at the extensive stage (8).

Mean age of the patients in our study was 62.4±9.8 years while the most common comorbidity was HT. Majority of the patients was at the extensive stage (29.2% at the limited stage, and 70.8% at the extensive stage). Patients at the extensive stage lived for a shorter period of time (Median time: 1.2 months). Median survival time for the patients at the limited stage was 11.6 months. Estimated median survival time for all the patients accounted for 7 months. 78.5% of exitus cases were

disease-related while 3.1% of them were non-disease related.

Smoking cessation is the most effective precaution for lung cancer to mitigate epidemics. Smoking cessation is important for the treatment no matterwhat stage a lung cancerpatient is at. Continuing smoking is related to recurrences and reduced survival for localized types of cancer and it increases the risk of contracting cancer for the second time. Smoking cessation decreases dyspneaand fatigueat all stages of cancer cases and increases appetite and life quality (9). Having carried out a retrospective study with 20561 lung cancer cases, Radzikowska et al. found out that the percentage of non-smokers were 4.3%. For SCLC cases, smoking percentages for men and women were 98.5% and 90.8%, respectively (10). Another study revealed that those smoking at the time of diagnosis and continuing to do so had a higher mortality (11). 93.8 % of the cases in our study were smokers. Cigarette pack/ year average was found to be 52.

Clinical stage at the time of diagnosis is one of the key prognostic factors. Limited stage seemed a better prognosis than the extensive stage. İncreasing number of metastasis at the extensive stage worsens the prognosis (12). Chen et al. argue that after restoring other known factors, low PS does not estimate the poor survival, and PS should not be the sole factor for therapy decisions (11). Clark et al. point out that a good performance score, female gender and limited stage are good prognostic factors (13). In addition, Foster et al. reveals in a study that the general survival and the progression-free survivalare the most important prognostic factors for all the patients. Patients at the extensive stage had a worse prognosis. In a multi-variable analysis, age and gender was extremely prognostic for the patients at the limited stage in terms of general survival andprogression-freesurvival. Advancedageand male gender proved a worse prognosis. Age, gender and PS were extremely prognostic for the patients at extensive stage in terms of general survival and progression-free survival. Patients with an advanced age, male gender and PS> 0 in particular were worse in general survival (14). There was no statistically significant difference in terms of age even though cases of exitus in our study were older. 70.7% of patients were at the extensive stage. 83% of cases of exitus were at the extensive stage. ECOP PS averages of cases of exitus on the follow-up were statistically high. No comparison was made between genders since the number of female patients was very few.

Hermes et al. showed in a study carried out with 395 cases that hyponatremia is an independent determinant of mortality for SCLC patients at advanced and early stages irrespective of age, gender, LDH and performance (15). Torun et al. found out in a univariate analysis that LDH, CA 15-3, GGT, SGOT, hyponatremia and a low performance score were poor prognostic factors (p = 0.024, 0.032, 0.047, 0.013, 0.021 and 0.013 respectively). However, they identified no significant difference when it came to a multivariate analysis. The stage was a prognostic factor for univariate and multivariate analyses (16).

Another study reveals that the major prognostic factor within the first 6 months following the inception of therapy is the ALP value. Serum Na, gamma-glutamyl transferase (GGT), albumin, urea, chlorine scores are less important. Serum Na scores are reported to be important for long-term prognosis (7).

Li et al. found out that PS 0-1, limited stage, normal serum carcinoembryonic antigen (CEA) and vascular endothelial growth factor (VEGF) were related to better response scores. Gender, disease extent, PS, serum CEA and VEGF level made a significant impact on general survival. In a multivariate analysis, independent prognostic factors were disease extent, PS, serum CEA and VEGF level. In addition, Prophylactic Cranial Irradiation (PCI) and the number of metastatic lesions were reported to be independent prognostic factors for patients at limited and extensive stages. Female gender was defined as a good prognostic factor to survive. Among prognostic factors for the limited stage are good PS, normal serum CEA, VEGF level and PCI. Among prognostic factors for extensive stage are good PS, a metastatic site, normal serum CEA and VEGF level (17).

AST and LDH were common for cases of exitus in our study while there was no statistically significant difference in terms of LDH, Na, AST, ALT and Ca scores. Mortality rate was higher for those with an advanced ECOG PS and at advanced stage.

Torun et al. found out in a study that 15% of the patients suffered from SVCS. No significant relation was detected between SVCS and prognosis (p= 0.903) (16). VCSS percentage was 6.2% in our study. No significant relation was detected between VCSS and prognosis.

Types of metastasis always leading to a shorter survival are liver and brain metastases (13) Another study points out that the most common metastatic sites are liver (17-34%), bones (19-41%), bone marrow (17-23%) and central nervous system (0-30%) (19).Among the metastatic sites in our study were liver for 30.8%, bone for 15.4%, brain for 12.3%, and others for 10.8% of the cases.

Bonemetastases point toa poor prognosisfor lung cancerpatients. Mortality rateincreasesfor majority of patients with a bone metastasis or a complication induced by bone involvement (19). Cases of exitus had an extremely high percentage of liver metastasis in our study.

In conclusion, our study could not prove through laboratory tests that LDH, Na, AST, ALT and Ca scores are independent prognostic factors. Age, pleural fluid and VCSS were not found out to be prognostic factors. Performance score, stage and liver metastasis were identified as significant factors which define the prognosis. Knowing about some prognostic factors at the time of diagnosis is extremely important to estimate clinical results for this type of cancer. In addition, gaining insight into the specific administration of therapy, response to treatment, and some predictive factors to know about toxicity are highly important for patient selection and post-therapy response expectations.

Patient's Consent: Written informed consent was not obtained due to the retrospective nature of the study.

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