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Prognostic indicators of survival in patients with small-cell lung cancer at a tertiary care center in Lebanon

Arafat Tfayli[1,2], Hanine Atwi[1], Amal Naji[1], Majd Al Assaad[1], Sahar Assi[3] and Maya Hazimeh[3]

Abstract

Objective: Small-cell lung cancer is a very aggressive tumor associated with high invasiveness and ease of metastasis and therefore poor prognosis. In the literature, several demographical, clinical as well as pathological factors including age, stage, gender and smoking were cited as independent prognosticators of survival.

Material and Methods: This is a retrospective cohort study that includes 222 patients diagnosed with small-cell lung cancer between 2010 and 2019. Clinical and demographic data were extracted from their medical records. The Kaplan–Meier and logistic regression models of statistical analysis were used to evaluate the association of these variables with survival.

Results: Forty-five percent of patients were found to be alive at the time of data collection. The median survival of patients with small-cell lung cancer was found to be 14 months. On univariate analysis, increasing age as well as stage (extensive disease) were found to be significantly associated with decreased survival at 3 years. On the contrary, both gender and smoking status at diagnosis were not shown to significantly influence survival. On multivariate analysis, both age as well as stage remained significantly associated with survival.

Conclusion: Limited data exist in the literature regarding the prognostic indicators of survival in small-cell lung cancer, especially from the Middle East area. In our study, both age and stage at the time of diagnosis were found to significantly influence survival. Further studies are needed to assess the association of other factors with survival.

Keywords
Small-cell lung cancer, survival, smoking, Lebanon

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide.[1] It accounts for around 9.2% of all newly diagnosed cancers in Lebanon.[2] It is classified into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC represents 15% of all lung cancer cases[3]. Despite the fact that the incidence of SCLC has decreased in the past decade, a drop attributed to a decrease in the prevalence of smoking;[4] it remains a serious health care problem. It is a disease characterized by high invasiveness, short doubling time, high growth fraction and ease of metastasis.[5,6] Therefore, most patients present with advanced, non-curable disease.

The median survival of patients with SCLC cited in the literature is reported to be around 7 months.[6] Despite its chemo-sensitivity and radiosensitivity, almost all patients relapse and die from this disease.[5]Smoking, radon and occupational exposure have been identified as possible risk factors of SCLC. Specifically, radon was found to significantly increase the risk of SCLC in a linear dose–response pattern.[7] Clinical, demographic as well as pathological factors were identified as important prognostic factors. These

[1]Division of Hematology and Oncology, Department of Internal Medicine, American University of Beirut, Beirut, Lebanon
[2]Naef K. Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon
[3]Faculty of Medicine, American University of Beirut, Beirut, Lebanon

Corresponding author:
Arafat Tfayli, Naef K. Basile Cancer Institute, American University of Beirut Medical Center, PO Box: 11-0236, Riad El Solh, Beirut 1107 2020, Lebanon.
Email: at35@aub.edu.lb

factors include but are not limited to presenting symptoms, age at the time of diagnosis, gender, ethnicity and stage at the time of diagnosis.[4,6,8]

In this study, we reviewed the records of 222 patients diagnosed with SCLC at a tertiary care center in Lebanon between 2010 and 2019. We aim to illustrate the association of the various SCLC patients' characteristics with long-term survival and thus prognosis. To our knowledge, this is the first study to report on clinical characteristics and prognostic factors of SCLC patients from the Middle East area.

Methods

This is a single-center retrospective study that involved the chart review of the clinical records of 222 patients diagnosed with SCLC between 2010 and 2019. After approval of the institutional review board (IRB) (protocol number NA12-02-2019, IRB ID: BIO-2018-0513), the hospital medical and electronic records of the patients were reviewed. Data were extracted from the medical records of the patients, and no interventions were performed. Oral informed consents were approved by IRB (protocol number NA12-02-2019, IRB ID: BIO-2018-0513) and were obtained from all the patients prior to study initiation. Patients were periodically called to determine their survival status.

The data that were extracted included age at diagnosis, smoking status at diagnosis, gender, symptoms at initial presentation, nationality, stage at diagnosis as well as survival status. The primary outcome of this study is to determine the overall survival of patients with limited as well as extensive stage SCLC. The secondary outcome of this study is to assess the association of age at diagnosis, gender, smoking status at diagnosis and stage at diagnosis with overall survival in SCLC patients. After obtaining oral informed consent, all patients diagnosed with SCLC, irrespective of the stage, were included. Patients diagnosed with NSCLC were therefore excluded. Statistical analysis was done using SPSS v24. Categorical variables were presented as percentages, while continuous variables were presented as mean and standard deviation.

Univariate analysis was done using the various clinical and demographic variables to determine their association with survival. Variables that were found to be significant in the univariate analysis were then run through multivariate analysis using logistic regression. Hazard ratio (HR) was reported as well as their 95% confidence intervals. Results were considered significant when P value was less than 0.05.

Results

Demographic, clinical and pathological characteristics

Data from the clinical records of 222 patients diagnosed with SCLC between 2010 and 2019 were analyzed (Table 1). The mean age at diagnosis was 65 ± 19.1 years; 79% of the patients were found to be older than 60 years, while only 21% were less than 60 years old. Most of the patients were Lebanese and males (75% and 68%, respectively). Most of the patients were either active (49%) or former smokers (37%). Only 2% of the patients smoked waterpipe.

Table 1. Clinical, demographic and pathological characteristics of 222 patients with SCLC.

Variable	Subgroup	N = 222 (%)
Mean age at diagnosis ± SD (years)		65.76 ± 19.1
Gender	Male	152 (68)
	Female	70 (32)
Age at diagnosis (years)	Less than 60	46 (21)
	More than 60	176 (79)
Nationality	Lebanese	167 (75)
	Non-Lebanese	55 (25)
Smoking status at diagnosis	Active smoker	108 (49)
	Former smoker	82 (37)
	Never smoker	18 (8)
	Unknown	14 (6)
	Waterpipe smoker	4 (2)
Presentation	None/Incidental	18 (8)
	Respiratory symptoms[a]	128 (58)
	Systemic symptoms[b]	13 (6)
	Weight loss	17 (8)
	Pain	44 (20)
	Unknown	46 (21)
Stage at diagnosis	Limited disease	65 (29)
	Extensive disease	157 (71)
Overall survival	Alive	99 (45)
	Dead	123 (55)

[a]Respiratory symptoms: cough, hemoptysis, dyspnea, upper respiratory tract infection.
[b]Systemic symptoms: weakness, fatigue, fever, night sweats, anorexia.

At the initial visit, patients presented with a wide range of symptoms. While only 8% were asymptomatic at the time of diagnosis, 58% of the patients had respiratory symptoms including cough, hemoptysis, dyspnea and upper respiratory tract infections. Six percent of the patients had systemic symptoms which included weakness, fatigue, night sweats and anorexia. Other common symptoms include pain (20%) and weight loss (8%). Most patients were found to have extensive disease (71%), while only 29% of the patients had limited disease.

Univariate analysis: factors influencing survival

Survival data were collected on 222 patients diagnosed with SCLC between 2010 and 2019 (Table 2). With a median follow-up of 29 months, 45% patients of the patients were found to be alive. The median survival time was 14 months.

The association of the various clinical and pathological factors with survival was studied using the Kaplan–Meier

method. Both age and stage at diagnosis were found to be significant predictors of survival at 3 years; 51.1% of patients less than 60 years were found to be alive at 3 years compared to 22.9% of patients more than 60 years of age (P = 0.003). More patients with limited disease were found to be alive at 3 years than patients with extensive disease (37.9% vs 24%) (P = 0.001). This can also be seen in Figure 1 which showed significant decrease in survival in patients with extensive disease when compared to limited disease. The median survival for limited stage SCLC was found to be 21 months in comparison to a duration of only 12 months in extensive disease

Conversely, both gender and smoking status at diagnosis were not found to be significantly associated with survival at 3 years. Therefore, females (35.8%) did not show superior survival when compared to males (25.2%) (P = 0.165). Moreover, patients who were active smokers or former smokers did not show decreased survival when compared to never smokers (P = 0.393).

Table 2. The association of the various clinical and demographic factors with survival at 3 years (univariate analysis).

Variable	Survival at 3 years (%)	P value
Age at diagnosis (years)		0.003*
Less than 60	51.1	
More than or equal to 60	22.9	
Gender		0.165
Male	25.2	
Female	35.8	
Smoking status at diagnosis		0.393
Never smoker	39.6	
Former smoker	25.6	
Active smoker	27.4	
Stage at diagnosis		0.001*
Limited disease	37.9	
Extensive disease	24	

*P < 0.05.

Multivariate analysis: the association of independent variables with survival

Variables (age and stage at diagnosis) that were found to be significant on univariate analysis were then run through multivariate analysis (Table 3). These two variables remained significantly associated with survival. Increasing age was found to be a significant and negative predictor survival with an HR of 1.048 (P < 0.001). Moreover, patients with limited disease showed superior survival when compared to patients with extensive disease (HR = 2.275, P < 0.001).

Discussion

SCLC is a highly aggressive tumor with poor prognosis. We found that the median survival of patients from the time of diagnosis till the time of death was 14 months. Several studies

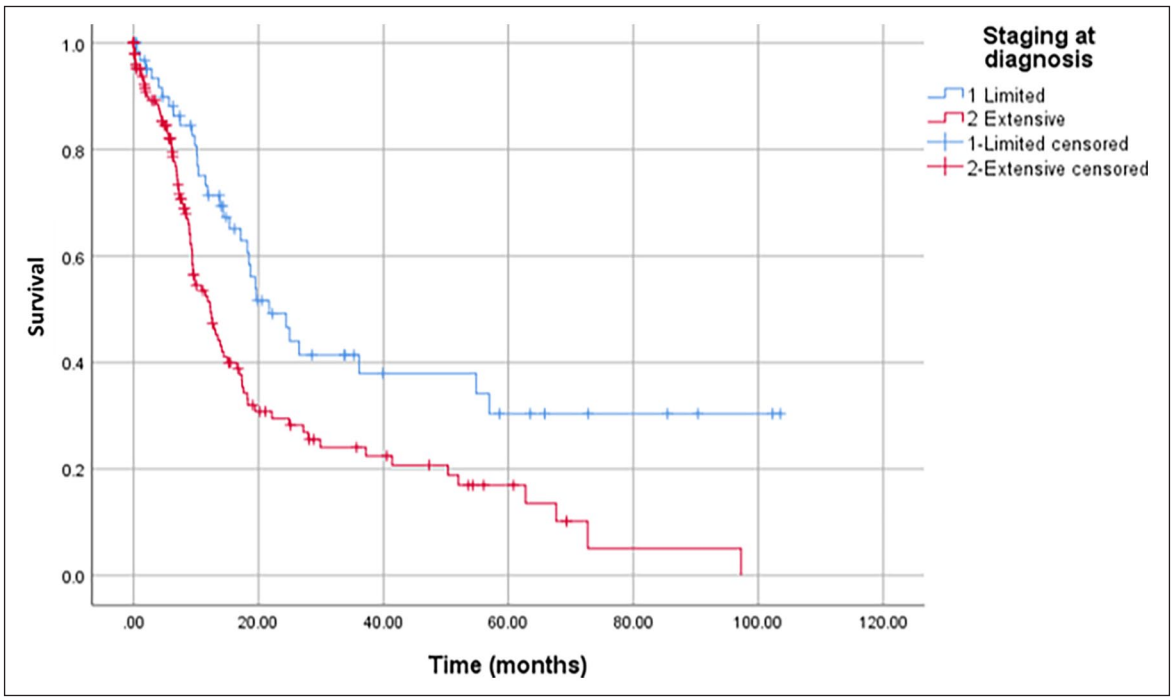

Figure 1. The correlation of survival in months with the stage at diagnosis (limited vs extensive disease).

Table 3. Independent factors influencing survival (multivariate analysis).

Variable	Hazard ratio	Lower 95% CI	Upper 95% CI	P value
Age at diagnosis	1.048	1.027	1.070	<0.001*
Stage at diagnosis				<0.001*
Limited stage	Reference			
Extensive stage	2.275	1.496	3.459	

CI: confidence interval.
*P < 0.05.

have attempted to understand the association of the various sociodemographic and clinical characteristics with overall survival in patients with SCLC. This is a retrospective study that aims to investigate these characteristics and is conducted in a tertiary care center in Lebanon.

Patients with SCLC usually present with non-specific symptoms. The non-specificity of the symptoms at the time of presentation significantly contributed to a delay in the diagnosis of lung cancer.[9] These symptoms include respiratory symptoms as cough, wheezing, hemoptysis as well as constitutional symptoms.[10] This was consistent with the results of our study which showed that the most frequent symptoms at the time of presentation were respiratory symptoms followed by systemic symptoms such as fever, fatigue, weakness and weight loss.

In our study, we found that 45% of the patients were found to be alive at the time of data collection. Both age at diagnosis and stage were found to be significant predictors of survival. We found that increasing age is associated with decreased survival; 51.1% of patients younger than 60 were alive after 3 years from the time of diagnosis compared to only 22.9% of the patients older than 60 years. This was consistent with most of the data in the literature. Patients younger than 70 years were found to have improved survival.[4] Moreover, improvement in survival was age dependent, especially in patients with extensive disease.[8] However, a study by Jara et al.[11] showed no difference in median survival and 1-year survival between patients older than 70 years and patients younger than 70 years.

Patients with SCLC are more likely to present with extensive disease at the time of diagnosis. In a study conducted by Jiang et al.,[12] two-thirds of the patients with SCLC had extensive disease at the time of diagnosis. Similarly, in our study, 71% of the patients had extensive disease SCLC. Extensive disease was shown to be associated with decreased survival as seen in Figure 1. This is consistent with data in the literature. The 5-year survival rate was approximately 10%–15% for patient with limited disease SCLC compared to 1%–2% for patients with extensive disease SCLC.[13] Consequently, extensive disease SCLC was found to be a negative predictor of survival.[14]

Gender and smoking status at diagnosis were not found to be significantly associated with survival. Data in the literature regarding the effect of gender on overall survival in SCLC have been inconsistent.[15,16] Several studies showed that women had significantly better survival outcomes when compared to men.[8,17] However, a cohort of patients with limited stage SCLC showed no association between gender and overall surviva.l[18] Moreover, a study by Paesmans et al.[19] concluded that the effect of gender on overall survival was not reproducible enough for it to be considered as a prognostic factor.

Most patients with SCLC were found to be either current smokers or active smokers at the time of diagnosis.[15] Smoking status was not found to be significantly associated with survival in our study. On the contrary, a study conducted by Makuch et al.[16] concluded that active smokers at the time of diagnosis had decreased survival. The results of this study, which show the importance of age and stage as prognostic indicators of survival, are consistent with those of the literature. However, the significance of this study lies in the fact that it presents the first data in the Lebanese population.

Limitations

One of the limitations of this study is that it is a single-center study with a relatively small sample size. Moreover, the smoking status of some of the patients was unknown at the time of data collection. Another limitation includes the fact that this study did not include measurement of the exposure of the patients to radon. Radon was identified as the second cause of lung cancer. Moreover, formal sample size calculation and power analysis were not performed. All patients diagnosed with SCLC were included. Several other potential therapeutic, molecular and genetic variables have been described in several studies in the literature, and these are not assessed in this retrospective study.

Conclusion

In conclusion, limited data exist in the literature regarding the prognostic indicators of survival in SCLC, especially from the Middle East area. Both age and stage at the time of diagnosis were found to be significant and independent prognosticators of survival in SCLC patients. Further studies are needed to evaluate other molecular, genetic and therapeutic predictors of survival in SCLC.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval

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Informed consent

Oral informed consent was obtained from all subjects before the study. Oral consents were approved by the institutional review board (IRB) (protocol number NA12-02-2019, IRB ID: BIO-2018-0513).

ORCID iDs

Arafat Tfayli https://orcid.org/0000-0002-0633-2538

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